Nonprostanoid Prostacyclin Mimetics. 2. 4,5-Diphenyloxazole Derivatives

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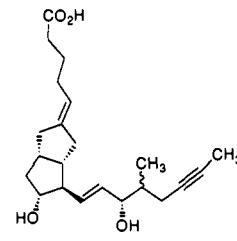
4,5-Diphenyl-2-oxazolenonanoic acid (**18b**) was synthesized and found to inhibit ADP-induced aggregation of human platelets with an IC_{50} of 2.5 μM. Acid **18b** displaced [^{3}H]iloprost from human platelet membranes in a concentration-dependent fashion, consistent with **18b** inhibiting platelet function by acting as a prostacyclin mimetic. By inserting a phenoxy ring into the side-chain moiety of **18b** and systematically varying the pattern of substitution and length of the tethers, more potent inhibitors of platelet aggregation were identified. A phenoxy ring inserted centrally in the side chain proved to be the optimal arrangement but significant activity was observed when the aromatic ring was bound directly to the 2 position of the heterocycle. The meta-substituted *cis*-(ethenylphenoxy)acetic acid **37** is the most potent platelet aggregation inhibitor synthesized as part of this study with an IC_{50} of 0.18 μM. Acid **37** displaces [^{3}H]iloprost from human platelet membranes with an IC_{50} of 6 nM. The *trans*-olefinic isomer of **37** (**25p**) is 72-fold weaker as an inhibitor of ADP-induced platelet aggregation, but the saturated derivative **25w** (BMY 42393) is intermediate in potency. Structure–activity studies using **25w** as a template focused on modification of the tethers intervening between the side-chain phenyl ring and the oxazole and carboxylate termini and substitution of the phenyl ring. These studies revealed that biological activity was sensitive to both the identity of the concatenating atoms and the pattern of ring substitution. The structure–activity relationships provide insight into the topographical relationship between the diphenylated oxazole ring and the carboxylic acid terminus that comprise the nonprostanoid prostacyclin mimetic pharmacophore.

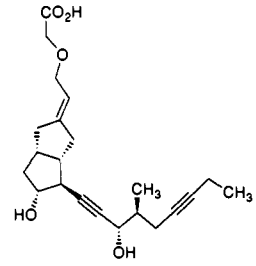
Introduction

Clinical studies conducted over the last decade with blood platelet aggregation inhibitors have provided evidence that platelet activation is involved in the etiology of arterial thrombosis.[1-6] These findings provide further impetus to identify and develop powerful and effective inhibitors of blood platelet function that might offer a significant advantage over the agents currently available to the clinician.[7,8] Metabolites of arachidonic acid (**1**) participate in the physiological regulation of hemostasis.[9] In endothelial cells, **1** is the biosynthetic precursor to prostacyclin[10] (PGI_2) (**2**), the most potent endogenous inhibitor of platelet aggregation yet identified that is also a powerful vasodilator (Scheme I). In contrast, activated platelets metabolize **1** to thromboxane A_2[11] (TxA_2) (**3**), a highly unstable compound with pharmacological properties opposite to those of PGI_2 (**2**). By constricting the blood vessel and recruiting platelets, TxA_2 is thought to participate in the development of hemostatic plugs at sites of vascular injury. With the discovery and structural elucidation of **2** and **3**, extensive effort was directed toward identifying effective PGI_2 mimetics and TxA_2 antagonists with the objectives of illuminating the physiological and pathophysiological roles of **2** and **3** and developing clinically useful antithrombotic agents. Although structurally diverse and relatively simple antagonists of TxA_2 have been described,[12] effective PGI_2 mimetics have generally retained the complex functionality that characterizes the natural product.[13] PGI_2 (**2**) is available for clinical use,[14] but it must be administered parenterally and produces an evanescent inhibition of platelet function due to its chemical instability.[15] Structurally similar but chemically stable analogues of **2** that have been advanced into clinical study include iloprost (**4**),[16] cicaprost (**5**),[17] beraprost (**6**),[18] and taprostene (**7**).[19]

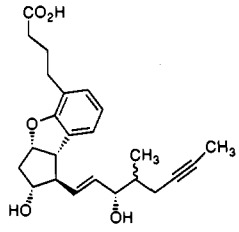
EP 035 (**8**) and EP 157 (**9**) were the first PGI_2 mimetics to be described that constituted a significant departure from previously developed structure–activity relationships, although these compounds are based on well-studied prostanoid-type skeletons.[20] The description of octimibate (**10**) as a PGI_2 mimetic represented a further structural simplification and provided an unusual template from which to design ligands for the PGI_2 receptor.[21,22] We



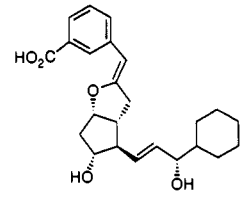
4, Iloprost



5, Cicaprost



6, Beraprost



7, Taprostene

† Department of Cardiovascular Biochemistry.

(1) Fuster, V.; Badimon, L.; Adams, P. C.; Turitto, V.; Cheseboro, J. Drugs Interfering with Platelet Functions: Mechanisms and Clinical Relevance. *Thrombosis and Haemostasis*; Verstraete, M.; Vermylen, J.; Lijnen, H. R., Arnout, J., Eds.; International Society on Thrombosis and Haemostasis and Leuven University Press: Leuven, 1987; pp 349–418.
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(3) Steering Committee of the Physicians' Health Study Research Group. Final Report on the Aspirin Component of the Ongoing Physicians' Health Study. *New Engl. J. Med.* **1989**, *321*, 129–135.
(4) Stein, B.; Fuster, V.; Israel, D. H.; Cohen, M.; Badimon, L.; Badimon, J. J.; Cheseboro, J. H. Platelet Inhibitor Agents in Cardiovascular Disease: An Update. *J. Am. Coll. Cardiol.* **1989**, *14*, 813–836.

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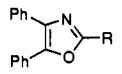
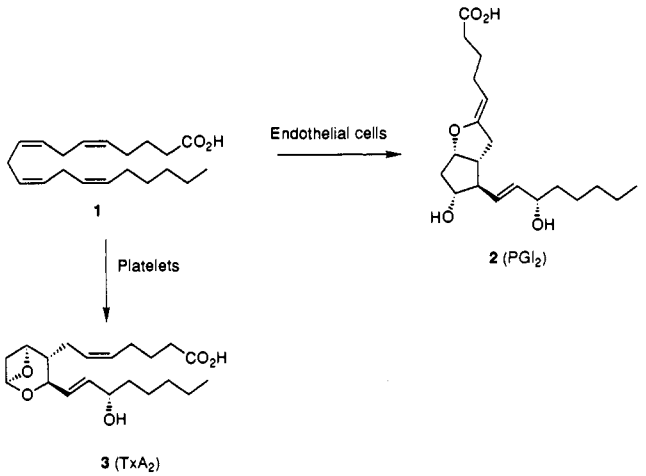
Table I. Physical Properties and Biological Activity Associated with 4,5-Diphenyloxazole-2-alkanoic Acid Derivatives



compd no.	R	mp, °C	anal.[a]	inhibition of ADP-induced human platelet aggregation: IC_{50}, μM[b]
17	$(CH_2)_7CH(CO_2H)_2$	115–117	$C_{25}H_{27}NO_5$	>76
18a	$(CH_2)_9CO_2H$	oil	$C_{25}H_{29}NO_3 \cdot 0.25H_2O$	>80
18b	$(CH_2)_8CO_2H$	83–85	$C_{24}H_{27}NO_3$	2.5
18c	$(CH_2)_7CO_2H$	70–73	$C_{23}H_{25}NO_3$	>88
18d	$(CH_2)_6CO_2H$	91–93	$C_{22}H_{23}NO_3$	>91
18e	$(CH_2)_4CO_2H$	127–128	$C_{20}H_{19}NO_3$	>100
18f	$(CH_2)_3CO_2H$	125–126	$C_{19}H_{17}NO_3$	>104
12	$(CH_2)_2CO_2H$	158–161	$C_{18}H_{15}NO_3$	>100

[a] Elemental analyses for C, H, and N are within ±0.4 of the theoretical values. [b] Blood platelet aggregometry was performed as previously described[21,23] and the results presented are the result of a single Experiment or the average of duplicates. Maximum variance (geometrical mean) was 65%. Octimibate displayed an IC_{50} of 1.02 μM under these conditions.[21]

Scheme I



defined the minimal structural elements necessary for binding to the platelet PGI_2 receptor and activating adenylate cyclase from an examination of a series of pyrazolealkanoic acid derivatives.[23] While the triphenylpyrazole

(5) Antiplatelet Trialists' Collaboration. Secondary Prevention of Vascular Disease by Prolonged Antiplatelet Treatment. *Br. Med. J.* 1988, *296*, 320–331.

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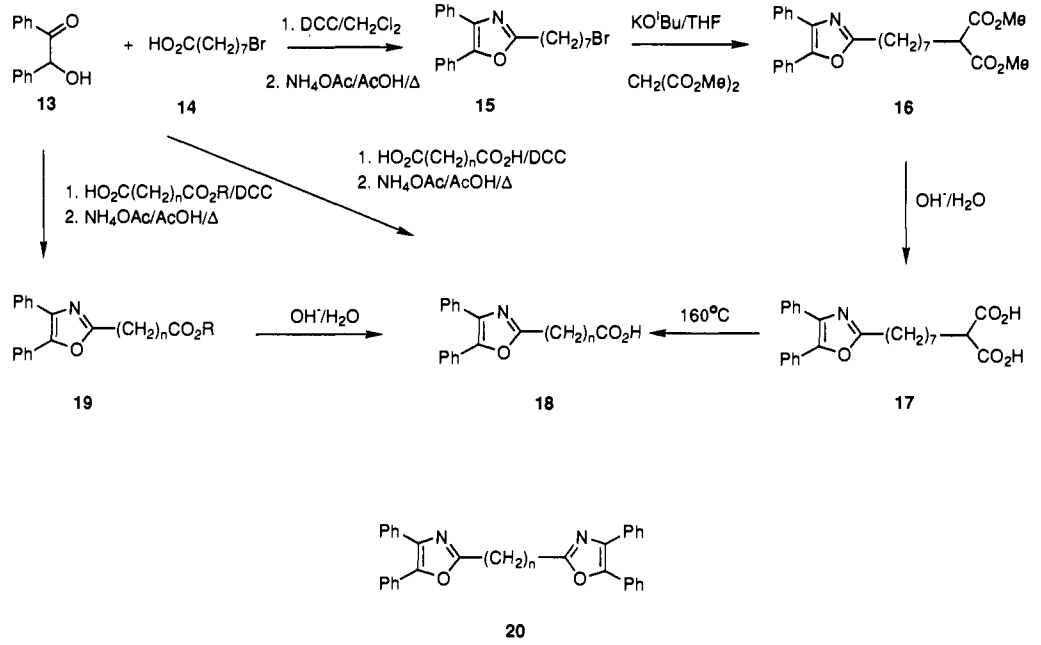
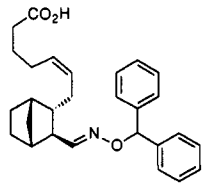
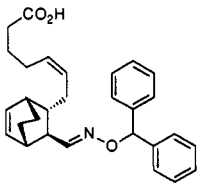
Scheme II



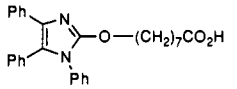
11a was the most potent PGI_2 agonist identified from that study, the diphenylpyrazoles **11b** and **11c** demonstrated significant platelet inhibitory activity.[23] In an animal model of thrombosis, **11a** provided superior antithrombotic protection compared to octimibate (**10**), but the duration of action of both compounds was less than desirable. Incorporation of an oxygen atom β to the carboxylic acid moiety of **11a**, to prevent β-oxidative degradation, offered minimal improvement and suggested that side-chain cleavage, by α-hydroxylation of the carbon atom adjacent to the heteroatom of the ring, may be responsible for the poor pharmacokinetic properties of **11a**. Consequently, we sought to identify a PGI_2 agonist of this structural class in which the heterocycle and side chain were connected through an all-carbon framework. We were attracted to the 4,5-diphenyloxazole ring system as a surrogate for the pyrazole of **11b** since this moiety is present in oxaprozin (**12**), an orally effective anti-inflammatory agent with a high degree of resistance to metabolic modification and an extended duration of action.[24] In this report, we demonstrate the functional equivalence of the oxazole and pyrazole ring systems in this class of nonprostanoid PGI_2 mimetic. Additionally, we describe the results of studies designed to provide insight into the topographical relationships within this pharmacophore. This effort has resulted in the identification of an orally effective PGI_2 mimetic that demonstrates antithrombotic activity in animal models and possesses a long duration of action in vivo.



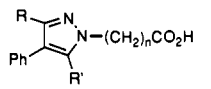
8, EP 035



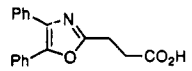
9, EP 157



10, Octimibate



11a, R = R' = Ph, n = 8
11b, R = Ph, R' = H, n = 8
11c, R = H, R' = Ph, n = 7



12, Oxaprozin

Chemistry

Scheme II depicts the synthetic approaches used to prepare 4,5-diphenyloxazoles substituted at the 2 position with simple alkanoic acid side chains. DCC-mediated coupling[25] of benzoin (**13**) with 8-bromooctanoic acid (**14**) followed by oxazole ring formation ($NH_4OAc/AcOH/\Delta/1$ h)[26] provided bromide **15**. Elaboration of **15** via a malonic ester synthesis[27] to the acid **18b** proceeded through the intermediacy of diester **16** and diacid **17**. A more direct procedure to prepare acids **18** involved acylation of **13** with

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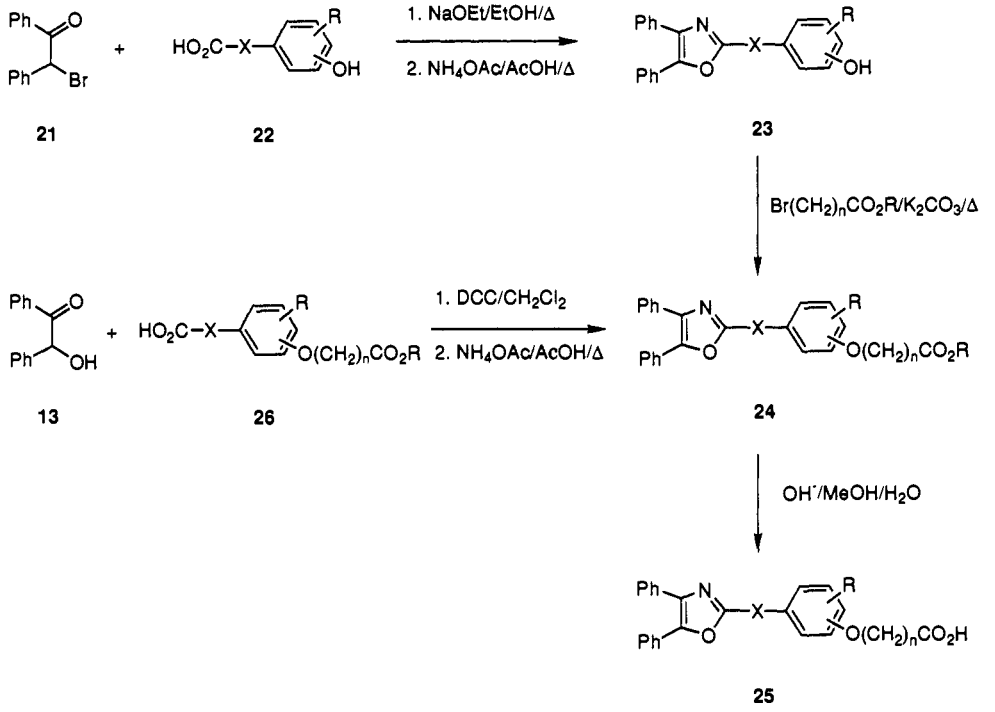
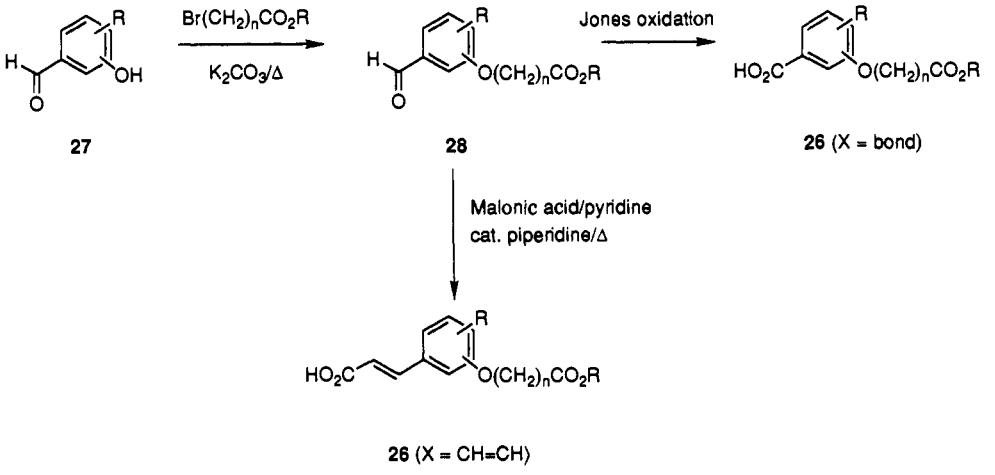
(27) House, H. O. *Modern Synthetic Reactions*, 2nd ed., W. A. Benjamin: Menlo Park, CA, 1972; pp 492–570, 586–595.

Scheme III



Scheme IV



the half-esters of dicarboxylic acids followed by heterocyclic ring construction, to give the esters **19**, followed by saponification. Where the half-esters were not readily available, coupling of a 3-fold excess of a diacid with **13** and subsequent oxazole formation provided the target acids **18** directly along with the bisoxazole derivatives **20**, which were separated by column chromatography. A sample of oxaprozin (**12**) was prepared according to the literature procedure.[29] The compounds prepared by these methods are listed in Table I.

The insertion of an aromatic ring at various points in the side chain was explored as a means of modulating conformational mobility and increasing the complementarity of these ligands for the PGI_2 receptor. Alkylation of phenol derivatives provided a convenient method of assembling the compounds required to probe this aspect of the pharmacophore and the synthetic routes employed are depicted in Schemes III–XI. The phenols **23** were obtained by alkylation of the sodium salt of acids **22** with desyl bromide (**21**) in EtOH at reflux[28] followed by heterocycle formation under standard conditions (Scheme III). Alkylation of **23** with ω-bromoalkanoic esters, using K_2CO_3 as the base, provided the esters **24**, which were hydrolyzed to the corresponding acids **25** with aqueous hydroxide. DCC-mediated coupling of carboxylic acid **26** (X = bond, *trans*-CH=CH, CH_2CH_2), in which the ester-containing side chain is already incorporated, with **13** followed by oxazole ring formation provided an alternative route to esters **24**. The double bond of the cinnamate-derived esters **24**, in which X = *trans*-CH=CH, was reduced by hydrogenation over Pd on charcoal. The acids required for the synthetic approaches summarized in Scheme III were prepared by the routes outlined in Scheme IV. Alkylation of a hydroxybenzaldehyde with the appropriate ω-bromoalkanoic ester furnished aldehyde **28**. Jones oxidation[30] of **28** gave acids **26** (X = bond) while homologation, by exposure to an excess of malonic acid in hot

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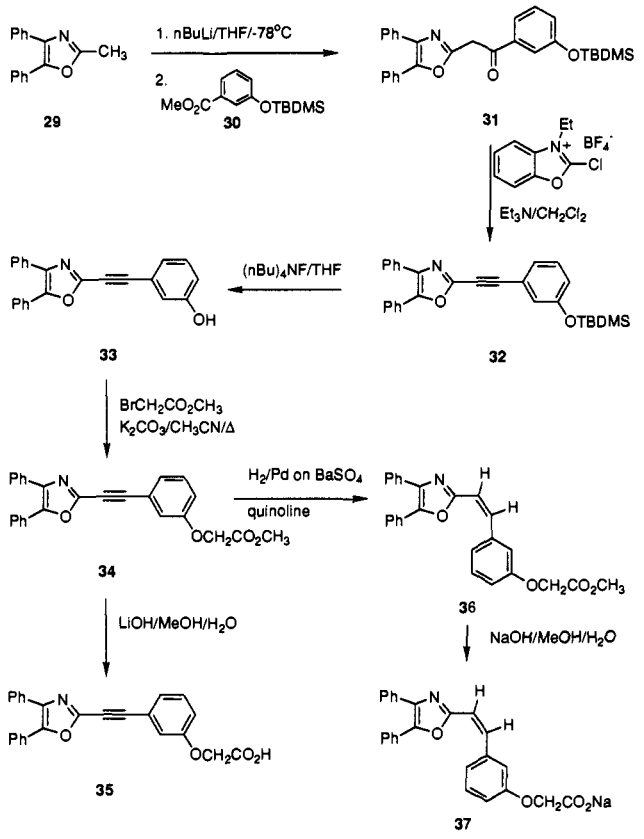
Scheme V

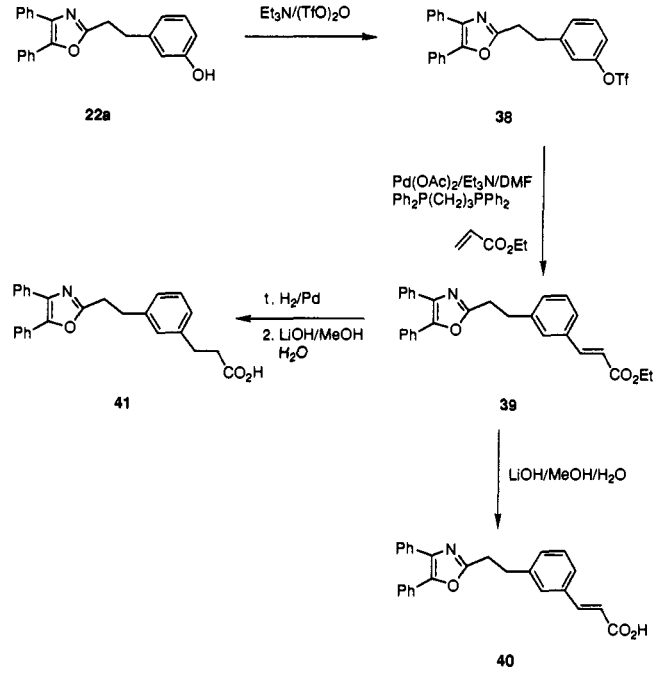


pyridine containing a catalytic amount of piperidine,[31] afforded the cinnamic acids **26** (X = *trans*-CH=CH). The methoxy-substituted benzaldehyde required as a synthetic precursor to **25r** and **25y** was obtained from commercial sources[32] while the isomeric aldehydes that served as progenitors of **25q/x** and **25s/z** were prepared using literature procedures.[33,34]

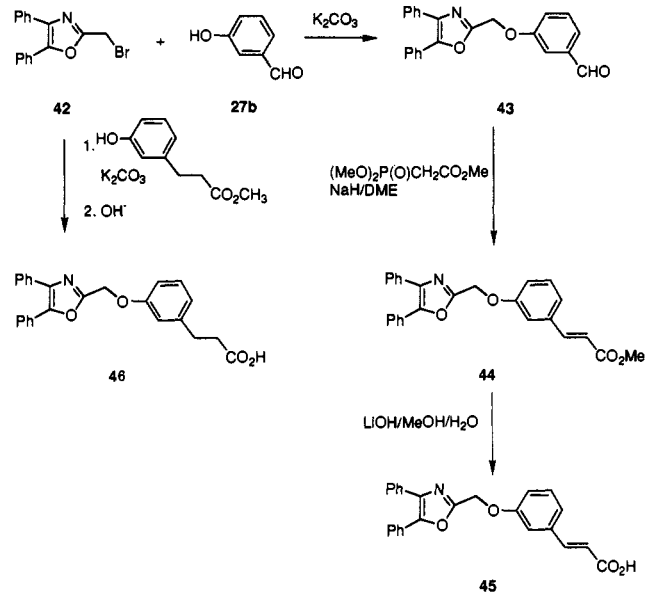
A number of structural variants of acid **25w** were synthesized in order to examine the impact of modifications to the skeleton of this compound on biological activity. Schemes V–XI summarize the synthetic procedures used to accomplish this phase of the study. The acetylene derivative **35** was prepared as depicted in Scheme V. Acylation of the anion derived from 2-methyl-4,5-diphenyloxazole (**29**)[25,35] with the benzoate **30**[36] provided ketone **31**, which existed as a 2.7:1 mixture of keto and enol forms in $CDCl_3$. Exposure of **31** to 2-chloro-3-ethylbenzoxazolium tetrafluoroborate in the presence of Et_3N[37] afforded the alkyne **32**, which was deprotected by treatment with fluoride to give phenol **33**. Alkylation of **33** with methyl bromoacetate followed by saponification gave target acid **35**. Catalytic hydrogenation of acetylene **34**, under carefully controlled reaction conditions, provided the *cis*-olefin ester **36** which was hydrolyzed with NaOH solution in MeOH to the acid salt **37**.

Replacement of the oxyacetic moiety of **25w** by a propionic acid-derived side chain was accomplished as described in Scheme VI. The phenol **22a** was converted to

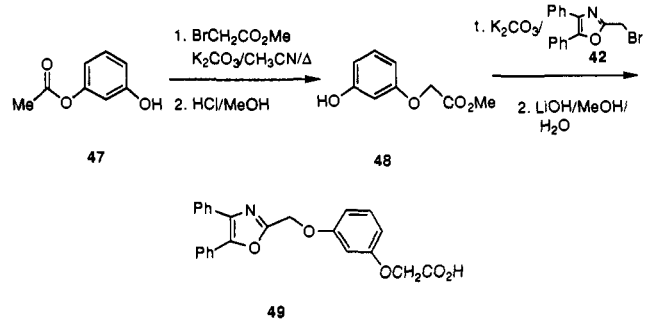
Scheme VI



Scheme VII



Scheme VIII



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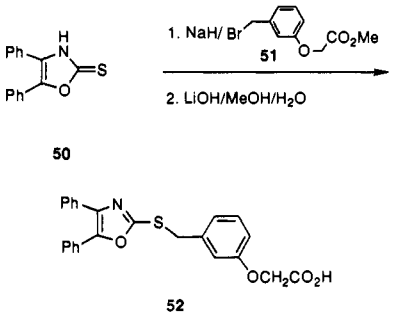
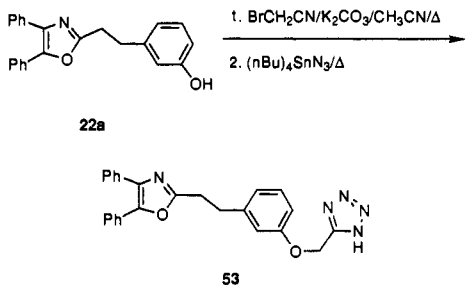
(37) Tsuji, T.; Watanabe, Y.; Mukaiyama, T. One Step Formation of Alkynes from Aryl Ketones. *Chem. Lett.* **1979**, 481–482.

Scheme IX



Scheme X

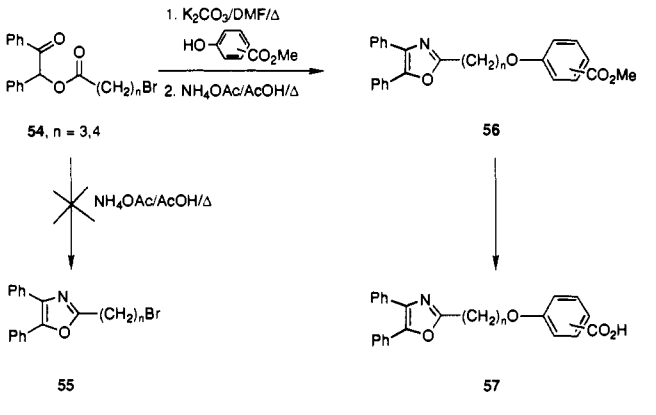


the corresponding triflate **38** and subjected to a Heck-type[38,39] coupling reaction with ethyl acrylate under the influence of palladium catalysis to yield ester **39**. Hydrolysis of **39** provided acid **40** while catalytic hydrogenation followed by saponification afforded the saturated acid **41**.

Variation of the tether between the oxazole and phenyl rings was achieved by the routes outlined in Schemes VII–IX. Alkylation of *m*-hydroxybenzaldehyde with bromide **42**[28] afforded oxazole **43**, which was homologated by a Wadsworth–Emmons reaction,[40] to give **44**, and saponified to acid **45** (Scheme VII). The saturated acid **46** was obtained by alkylation of methyl 3-(3-hydroxyphenyl)propanoate with bromide **42** followed by hydrolysis with aqueous NaOH. The synthesis of diether **49** began with alkylation of phenol **47** with methyl bromoacetate and was followed by dissolution of the crude product in acidic MeOH to furnish the phenol **48** (Scheme VIII). Alkylation of this material with the bromide **42** and subsequent saponification gave target acid **49**. The sulfide **52** was obtained by alkylation of thione **50**[41] with benzyl bromide **51**[42] followed by hydrolysis of the ester, as shown in Scheme IX.

The carboxy terminus of **25w** was replaced with a tetrazole moiety using the two-step sequence outlined in Scheme X. Alkylation of the phenol **22a** with bromoacetonitrile was followed by heating with tri-*n*-butyltin azide[43] to afford the target compound **53** after treatment

Scheme XI



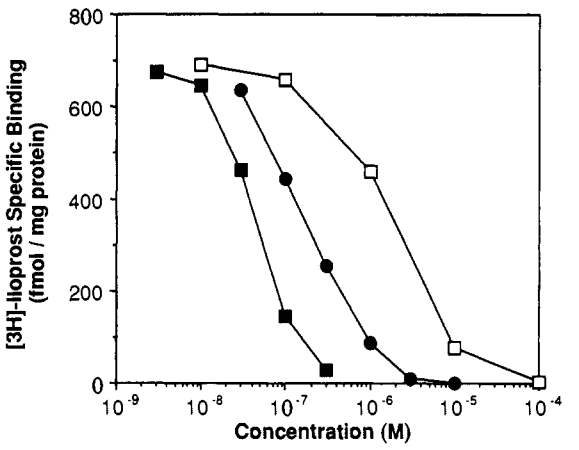


Figure 1. The effects of cold iloprost (**4**) (■), **18b** (□), and **25w** (●) on [^{3}H]iloprost binding to isolated platelet membranes. Each point represents the average of duplicate determinations within a representative experiment. The specific binding without any competing ligand was 655 fmol/mg protein. The experiments were performed as previously described.[21,23]

of the crude product with fluoride.

An aromatic ring was installed directly adjacent to the carboxylate terminal as shown in Scheme XI. Cyclization of the bromo esters **54** gave an intractable mixture rather than oxazoles **55**, presumably due to the increased kinetic propensity for intramolecular alkylation compared with the higher homologue **15**.[44] However, alkylation of the appropriate methyl hydroxybenzoate with the crude bromides **54** followed by heterocycle formation circumvented this problem and provided access to esters **56**. These were converted to the target acids **57** using aqueous hydroxide in MeOH.

The compounds prepared by the methods described in Schemes III–XI are listed in Table II along with relevant physicochemical data.

Results and Discussion

The target compounds were evaluated as inhibitors of ADP-induced aggregation of blood platelets in human platelet-rich plasma (PRP) according to the experimental protocol described previously[21,23] and the results are presented in Tables I and II. In this assay, PGI_2, iloprost, and octimibate exhibit IC_{50}'s of 8 nM, 2 nM, and 1.02 μM, respectively. Select compounds were also evaluated as inhibitors of collagen-induced aggregation in human PRP under conditions described earlier.[21]

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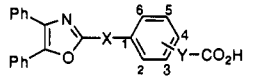
(41) Gompper, R. Investigations in the Azole Series. II. Preparation and Properties of Oxazole-2-thiones. *Chem. Ber.* **1956**, *89*, 1762–1768.
(42) Bromide **51** was prepared from *m*-hydroxybenzaldehyde by a sequence of alkylation ($BrCH_2CO_2CH_3/K_2CO_3/CH_3CN$/reflux), reduction ($NaBH_4$/MeOH), and bromination ($Ph_3P/CBr_4/CH_2Cl_2$).
(43) Kraus, J. L. Strategies to Synthesize a New Glyphosate Tetrazole Analogue. *Synth. Commun.* **1986**, *16*, 827–832.
(44) Hassner, A.; Fischer, B. Intramolecular Formation of Oxazolium Salts and their Reaction with N- and C-Nucleophiles. *Tetrahedron Lett.* **1990**, *31*, 7213–7214.

Table II. Physical Properties and Biological Activity of 4,5-Diphenyloxazole Derivatives



compd no.	X	Y	posn of Y on ring	ring subst	mp, °C	anal.[a]	inhibition of ADP-induced human platelet aggregation: IC_{50}, μM[b]
25a	bond	$O(CH_2)_4$	4		163–165	$C_{26}H_{23}NO_4$	>77
25b	bond	$O(CH_2)_3$	4		163–165	$C_{25}H_{21}NO_4$	>80
25c	bond	$O(CH_2)_4$	3		111–113	$C_{26}H_{23}NO_4$	4.6
25d	bond	$O(CH_2)_3$	3		125–127	$C_{25}H_{21}NO_4$	80
25e	bond	OCH_2	3		213–215	$C_{23}H_{17}NO_4 \cdot 0.2EtOH$	>84
25f	bond	$O(CH_2)_4$	2		resin	$C_{26}H_{23}NO_4 \cdot 0.2H_2O$	>77
25g	bond	$O(CH_2)_3$	2		113–115	$C_{25}H_{21}NO_4$	>80
25h	CH_2	$O(CH_2)_3$	4		128–129.5	$C_{26}H_{23}NO_4 \cdot 0.35H_2O$	>76
25i	CH_2	OCH_2	4		152–152.5	$C_{24}H_{19}NO_4 \cdot 0.1H_2O$	>82
25j	CH_2	$O(CH_2)_3$	3		oil	$C_{26}H_{23}NO_4 \cdot 0.5H_2O$	>76
25k	CH_2	OCH_2	3		120–122	$C_{24}H_{19}NO_4 \cdot 0.1H_2O$	>82
25l	CH_2	$O(CH_2)_4$	2		oil	$C_{27}H_{25}NO_4 \cdot 0.2H_2O$	>74
25m	*t*-CH=CH	$O(CH_2)_3$	4		155–157	$C_{27}H_{23}NO_4 \cdot 0.1H_2O$	>75
25n	*t*-CH=CH	OCH_2	4		223–225	$C_{25}H_{19}NO_4$	10
25o	*t*-CH=CH	$O(CH_2)_3$	3		152–155	$C_{27}H_{23}NO_4 \cdot 0.1H_2O$	>75
25p	*t*-CH=CH	OCH_2	3		213–215	$C_{25}H_{19}NO_4$	13
25q	*t*-CH=CH	OCH_2	3	2-OCH_3	183.5–185	$C_{26}H_{21}NO_5 \cdot 0.4H_2O$	0.5
25r	*t*-CH=CH	OCH_2	3	4-OCH_3	194–197	$C_{26}H_{21}NO_5$	>75
25s	*t*-CH=CH	OCH_2	3	6-OCH_3	204–207	$C_{26}H_{21}NO_5$	>75
25t	*t*-CH=CH	$O(CH_2)_3$	2		135–136	$C_{27}H_{23}NO_4$	>75
25u	*t*-CH=CH	OCH_2	2		185–186.5	$C_{25}H_{19}NO_4$	>80
25v	CH_2CH_2	OCH_2	4		147–149	$C_{25}H_{21}NO_4$	9
25w	CH_2CH_2	OCH_2	3		153–154.5	$C_{25}H_{21}NO_4$	1.2
25x	CH_2CH_2	OCH_2	3	2-OCH_3	resin	$C_{26}H_{23}NO_5 \cdot 0.2H_2O$	1.4
25y	CH_2CH_2	OCH_2	3	4-OCH_3	139–141	$C_{26}H_{23}NO_5$	>75
25z	CH_2CH_2	OCH_2	3	6-OCH_3	160–162	$C_{26}H_{23}NO_5 \cdot 0.25H_2O$	>75
25aa	CH_2CH_2	$O(CH_2)_3$	2		resin	$C_{27}H_{25}NO_4$	>75
25ab	CH_2CH_2	OCH_2	2		60–64	$C_{25}H_{21}NO_4$	>80
25ac	CH_2CH_2	$OCH(CH_3)$	3		55–58	$C_{26}H_{23}NO_4 \cdot 0.25H_2O$	4
25ad	CH_2CH_2	$OC(CH_3)_2$	3		oil	$C_{27}H_{25}NO_4 \cdot 0.1H_2O$	>75
35	C≡C	OCH_2	3		164	$C_{25}H_{17}NO_4$	60
37	*c*-CH=CH	OCH_2	3		indistinct	$C_{25}H_{18}NO_4Na \cdot 1.45H_2O$	0.18
40	CH_2CH_2	*t*-CH=CH	3		114–115.5	$C_{26}H_{21}NO_3$	0.66
41	CH_2CH_2	CH_2CH_2	3		119–120	$C_{26}H_{23}NO_3$	16
45	CH_2O	*t*-CH=CH	3		145–147	$C_{25}H_{19}NO_4 \cdot 0.1H_2O$	14
46	CH_2O	CH_2CH_2	3		118–120	$C_{25}H_{21}NO_4 \cdot 0.1H_2O$	>80
49	CH_2O	OCH_2	3		133–135	$C_{24}H_{19}NO_5 \cdot 0.6H_2O$	1.2
52	SCH_2	OCH_2	3		136–137	$C_{24}H_{19}NO_4S$	9.6
53	CH_2CH_2	OCH_2CN_4H[c]	3		138.5–140	$C_{25}H_{21}N_5O_2$	1.5
57a	$(CH_2)_4O$	bond	4		150–153	$C_{26}H_{23}NO_4$	>77
57b	$(CH_2)_3O$	bond	4		181–183	$C_{25}H_{21}NO_4$	40
57c	$(CH_2)_4O$	bond	3		120–123	$C_{26}H_{23}NO_4$	>77
57d	$(CH_2)_3O$	bond	3		109–111	$C_{25}H_{21}NO_4$	>80

[a] Elemental analyses for C, H, and N are within ±0.4 of the theoretical values. [b] See footnote *b*, Table I. [c] YCO_2H is replaced by OCH_2CN_4H.

Within the series of alkanoic acid derivatives listed in Table I, only the nonanoate **18b** exhibits a significant inhibitory effect on platelet aggregation induced by ADP. This compound is comparable in potency to the structurally analogous pyrazole **11b** and is also an effective inhibitor of collagen-induced platelet aggregation with an IC_{50} of 3.7 μM. However, the effects of **18b** show some species dependence since it is a poor inhibitor of ADP-induced aggregation of rabbit platelets with an IC_{50} in excess of 85 μM. This is a profile similar to that observed with both octimibate (**10**)[21,22] and the pyrazole **11a**[23] and seems to be characteristic of this class of PGI_2 mimetic.[20] The biochemical properties of **18b** are consistent with a PGI_2-mimetic mode of action. In human platelet membranes, **18b** displaces [^{3}H]iloprost in a concentration-dependent fashion as shown in Figure 1. Although **18b** is a potent stimulator of adenylate cyclase in human platelet membranes,[45] the maximal effect is less than that recorded for PGE_1, which is known to bind to the PGI_2 receptor and stimulate adenylate cyclase. The acid **18b** can therefore be classified as a partial agonist at the PGI_2 receptor. The IC_{50} of 100 nM[45] for stimulation of adenylate cyclase by **18b** compares favorably with the affinity of the compound for the PGI_2/PGE_1 receptor determined from the ligand binding studies. However, the platelet inhibitory effects of **18b** are manifest only at much higher concentrations, presumably a consequence of binding to the plasma proteins present in the PRP used for this assay.[23]

The structure–activity correlates apparent from an examination of Table I clearly demonstrate that biological activity is dependent on side-chain length. Homologation of the alkanoic chain of **18b** by a single carbon atom in either direction (**18a** and **18c**) leads to a complete loss of platelet inhibitory properties, a pattern analogous to that observed with the pyrazole series described earlier.[23] The malonic acid derivative **17** is also inactive, demonstrating specificity for a single carboxylate moiety at the side-chain terminus. Although oxaprozin (**12**) was not expected to interfere with ADP-induced platelet aggregation based on its mechanism of action,[24a] in our hands it was also sur-

(45) Seiler, S. M. Unpublished data.

prisingly inefficient as an inhibitor of collagen-induced blood platelet aggregation with $IC_{50} > 100$ μM.

Having established that the 4,5-diphenyloxazole ring system is associated with effective PGI_2 mimicry, we sought to increase the intrinsic potency of **18b** by structural manipulation of the acid-containing side chain. It was anticipated that such a study would help to further define the topology of the nonprostanoid PGI_2 mimetic pharmacophore and provide some insight into important topographical relationships. To this end, a phenyl ring was installed at various points within the side chain, in order to restrict conformational mobility, and both the pattern of substitution and the length of the tethers were systematically varied. An examination of the data presented in Table II reveals that biological activity is retained with several of these structural modifications, but potency is highly dependent upon the spatial relationship between the diphenyloxazole moiety and the carboxylic acid functionality. For the 2-phenylated series **25a–g**, the meta-substituted pentanoate **25c** prevents ADP-induced platelet aggregation with efficacy similar to that of the prototypical compound **18b**, but the shorter butyric acid derivative **25d** is over 15-fold weaker. In addition, acid **25c** inhibits collagen-induced human platelet aggregation with an IC_{50} of 2.7 μM but does not prevent ADP-induced aggregation in rabbit PRP where $IC_{50} > 77$ μM. The meta relationship between the phenyl ring substituents for the series **25a–g** is clearly optimal and, notably, the number of atoms separating the oxazole ring and carboxylic acid moiety in **25c** is identical to that in **18b**.

Separation of the heterocyclic and phenoxy rings by a single methylene unit gave a series of compounds uniformly unimpressive as platelet aggregation inhibitors, regardless of the length of the acid-containing side chain or its site of attachment (**25h–l**). Although it is conceivable that the optimum combination of chain length and substitution pattern is not represented, studies with this series were not pursued further.

Potent platelet inhibitory activity is associated with compounds in which a two-atom tether intervenes between the side-chain aromatic ring and the oxazole heterocycle. Indeed, several representatives of this series offer a significant potency advantage over the parent molecule **18b**. With a *trans*-olefin bridge, the para- and meta-substituted phenoxyacetic acids **25n** and **25p**, respectively, inhibit ADP-induced aggregation with efficacy 4–5-fold weaker than that of the simpler nonanoate **18b**. The meta-disposed acid **25p** also effectively prevents collagen-induced platelet aggregation with an IC_{50} of 1 μM but is essentially inactive versus ADP in rabbit PRP where the IC_{50} is in excess of 70 μM. Modifications of the olefinic tether of **25p** revealed that potency is markedly dependent on geometry. The more linear alkyne **35** is 4-fold less effective than the prototype but the *cis*-olefin **37** is almost 2 orders of magnitude more potent than **25p**. Indeed, with an IC_{50} of 0.18 μM, **37** is the most effective platelet aggregation inhibitor to be identified from this study. That the platelet inhibitory properties of **35** and **37** correlate with affinity for the platelet PGI_2 receptor is demonstrated in Figure 2. *cis*-Olefin **37** potently displaces [^{3}H]iloprost from human platelet membranes with an IC_{50} of 6 nM, which compares with an IC_{50} of 40 nM for unlabeled iloprost in the same experiment. In contrast, the acetylene **35** is considerably weaker with an IC_{50} in excess of 10 μM.

For the series of *trans*-olefins, the oxyacetic acid side chain found in **25n** and **25p** appears to be optimal since the doubly homolgated congeners, butyric acid derivatives **25m** and **25o**, respectively, are inactive. Altering the

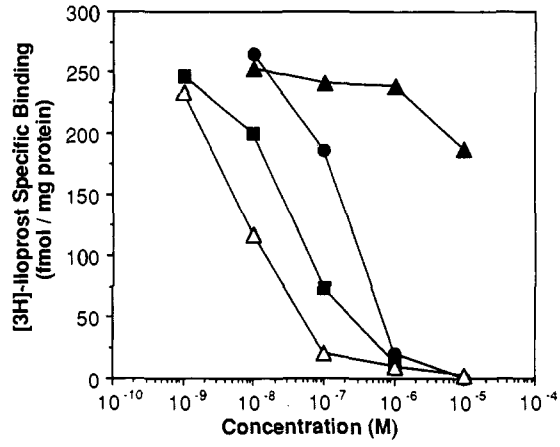


Figure 2. The effects of cold iloprost (**4**) (■), **35** (▲), **37** (△), and **25w** (●) on [^{3}H]iloprost binding to isolated platelet membranes. Iloprost binding was performed as described[21,23] except that the incubation was carried out at 37 °C for 30 min. Each point represents the average of duplicate determinations within a representative experiment. The specific binding without any competing compound present was 265 fmol/mg protein.

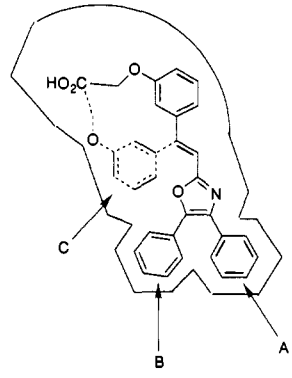


Figure 3. Two-dimensional representation of acids **25p** and **37** fitted into the nonprostanoid PGI_2 mimetic pharmacophore model proposed earlier.[23] The two heterocycle-bound phenyl rings are depicted as coplanar with the oxazole ring for purposes of convenience only and are not intended to suggest a conformational preference.

pattern of substitution about the phenyl ring to an ortho arrangement provided ineffective platelet inhibitors (**25t** and **25u**), irrespective of side-chain length, indicating some preference for an extended conformation. However, **25u** is a reasonable inhibitor of collagen-induced platelet aggregation with an IC_{50} of 27 μM. This is a property characteristic of agents that interfere with arachidonic acid mobilization and metabolism[46] and may be the result of an inhibition of platelet cyclooxygenase by **25u**. The structural arrangement of a diphenylated heterocycle proximate to a carboxylic acid moiety inherent to **25u** is compatible with the pharmacophore developed from studies of structurally diverse cyclooxygenase inhibitors.[47]

(46) Seiss, W. Molecular Mechanisms of Platelet Activation. *Physiol. Rev.* **1989**, *69*, 58–178.

(47) (a) Gund, P.; Shen, T. Y. A Model for the Prostaglandin Synthetase Cyclooxygenation Site and Its Inhibition by Anti-inflammatory Arylacetic Acids. *J. Med. Chem.* **1977**, *20*, 1146–1152. (b) Appleton, R. A.; Brown, K. Conformational Requirements at the Prostaglandin Cyclooxygenase Receptor Site: A Template for Designing Non-steroidal Anti-inflammatory Drugs. *Prostaglandins*, **1979**, *18*, 29–33. (c) Brown, K.; Cavalla, J. F.; Green, D.; Wilson, A. B. Diaryloxazole and Diarylthiazolealkanoic Acids: Two Novel Series of Non-steroidal Anti-inflammatory Agents. *Nature* **1968**, *219*, 164. (d) KB-T-3022. *Drugs Future* **1991**, *16*, 105–107.

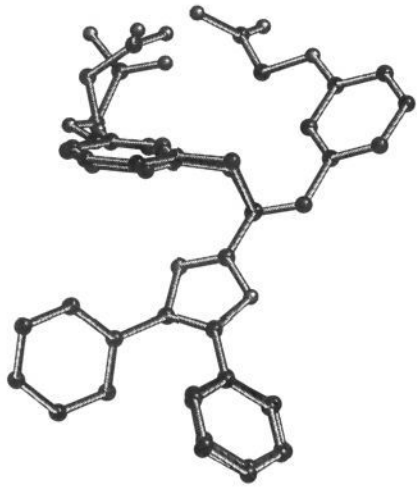


Figure 4. Energy-minimized conformations of acids **25p**, **25w**, and **37** generated using the SYBYL[48] molecular modeling program.

The structure–activity relationships that have emerged from this study can be broadly understood in terms of the pharmacophore deduced from evaluation of a series of di- and triphenylated pyrazolealkanoic acid PGI_2 mimetics.[23] The patterns of biological activity associated with the series of acids **25a–u**, **35**, and **37** are consistent with a nonlinear topology for this structural class of PGI_2 agonist and Figure 3 presents a simple two-dimensional representation of **25p** and **37** fitted into the receptor model developed earlier.[23] This proposal accommodates good overlap of the diphenylated heterocycle and carboxylate moieties but places the phenoxy rings of the two compounds in quite different environments within the pharmacophore. The phenoxy ring of the para-substituted olefin **25n** presumably fills the unoccupied region between **25p** and **37**, although probably with some deviation of the diphenyloxazole moiety from that shown in Figure 3. The markedly enhanced potency of the *cis*-olefin **37** compared to the trans-isomer **25p** is indicative of increased receptor complementarity. The mode of binding suggested in Figure 3 places the side-chain phenyl ring of **37** in the region putatively occupied by one of the heterocycle-bound phenyl rings of octimibate (**10**) or pyrazole **11a** and is designated as site C. Results from the earlier study[23] suggested that ligands occupying the C region demonstrated enhanced receptor affinity and platelet inhibitory activity. While this may account for some of the differences in potency between **25p** and **37**, the torsional distortions induced by nonbonded interactions between the substituents bound to the cis-olefinic bond of **37** are likely to provide a significant contribution. The conformational restrictions inherent to **37** suggests that the carboxylate binding site is located above (or below, depending on receptor chirality) the plane of the oxazole heterocycle. Figure 4 shows overlap of energy-minimized conformations of **25p** and **37**, generated using the SYBYL[48] molecular modeling program, that illustrates the proximity of the carboxy terminii of the two compounds when configured as proposed in Figure 3.

Further support for such a topographical relationship was obtained by exploring the effects of strategic introduction of an aryl ring substituent using the *trans*-olefin **25p** as a template. The 2, 4, and 6 positions of the phenoxy ring (as numbered in Table II) were selected as suitable sites since these patterns of substitution would be expected to exert significant and selective influence on the conformational preferences of the two side chains. For the series of methoxy-substituted compounds **25q–s**, only the 2-substituted isomer **25q**, in which the methoxyl is ortho to both of the ring substituents and projects into the C region (in the conformation presented in Figure 3), exhibits significant biological activity. This compound is over 1 order of magnitude more potent than **25p** while the isomeric compounds **25r** and **25s** appear to be at least 1 order of magnitude weaker than the parent structure. The potent activity observed for **25q** is consistent with the model of pharmacophore structure discussed above in which the relationship between the diphenylated heterocycle and carboxylate terminus deviates significantly from planarity. The effects of nonbonded interactions between the 2-methoxyl substituent and both the vinylic proton of the olefinic tether and oxyacetic acid side chain of **25q** would be expected to distort the phenoxy ring out of the plane of the heterocycle and influence the relative location of the carboxylate moiety. In the case of **25q**, this appears to result in markedly enhanced receptor complementarity, but this is obviously not true for the 6-methoxy isomer **25s**, where qualitatively similar effects on the conformation of the phenoxy ring might be anticipated. The poor activity observed for **25s** may reflect unfavorable steric repulsions if the methoxy substituent protrudes beyond the perimeter of the receptor when the molecule is bound in a fashion analogous to that proposed for **25p** in Figure 3. An alternative orientation, in which the methoxy group of **25s** projects into the C region of the receptor model, would place the ring substituent adjacent to the proton of the olefin tether rather than the olefinic bond itself. Although this arrangement would minimize nonbonded interactions, the relative spatial location of the carboxylate terminus in **25s** would be dramatically altered compared to that in **25q**. The poor activity associated with the 4-methoxy-substituted compound **25r** is more difficult to explain based on the above arguments but may provide another indication of the boundary of the receptor.

Saturation of the olefinic bonds in **25n** and **25p** revealed a divergence in structure–activity relationships for the different substituent patterns and provided further indication of receptor asymmetry. The para-substituted alkane **25v** is not significantly different from its oxidized progenitor **25n** as an inhibitor of ADP-induced platelet aggregation but, in contrast, the meta isomer, **25w**, is 10-fold more potent than the structurally related olefin **25p**. In addition to further defining receptor asymmetry, these observations are compatible with the topographical relationships developed above. Relief of the stereoelectronic constraints imposed by the extended π system in **25p** would allow the carboxylic acid terminus of **25w** to more effectively interact with the complementary recognition elements within the receptor protein if they are located in a different plane. In addition, the conformational flexibility inherent in the saturated acid **25w** would allow it to adopt a conformation more closely mimicking that of the *cis*-olefin **37**. Overlap of an energy-minimized conformation[48] of **25w** with **37** is illustrated in Figure 4. The increased platelet inhibitory activity of **25w**, compared to the simpler prototype **18b**, is reflected in enhanced affinity for the platelet PGI_2 receptor, as shown in Figure 2, and increased potency as a stimulator of platelet membrane adenylate cyclase, IC_{50} = 30 nM.[49] However, like previous members of this structural type of PGI_2 mimetic,[20–23] **25w** is a partial agonist compared to PGE_1 as a stimulator of the cyclase enzyme.[49]

(48) Tripos Associates Inc, St. Louis, MO. Version 5.4.

The effects of methoxy substitution in this saturated series (**25x–z**) are qualitatively similar to that observed with the unsaturated congeners **25q–s**. Thus, **25y** and **25z** are ineffective inhibitors of platelet function like their unsaturated relatives **25r** and **25s**, respectively. However, the marked increase in potency observed with **25q**, compared to **25p**, is not reproduced in the saturated series since the methoxy-substituted compound **25x** is equipotent with the unsubstituted analogue **25w**. This suggests that for the pair of unsaturated compounds **25p** and **25q**, the enhancement in potency seen upon substitution of the phenyl ring results primarily from torsional changes between the phenoxy ring and the olefin rather than a more direct effect on the relative spatial location of the carboxy terminus.

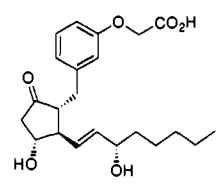
The effects of modification of the backbone upon biological potency were examined using the acid **25w** as the prototype and this study revealed some interesting structure–activity correlates. Activity was retained upon replacement of the oxyacetic acid moiety by a *trans*-propenoate (**40**) but the saturated derivative **41** expresses significantly weaker platelet inhibitory properties. While the removal of a potential hydrogen-bond acceptor can have profound effects on molecular recognition,[50] this would not appear to provide a satisfactory explanation for the case at hand. The introduction of an oxygen atom β to the carboxylate functionality does not enhance potency in this class of PGI_2 mimetic[23] or those based more closely on the natural prostanoid.[17] A more plausible explanation relies upon variations in side-chain conformation influenced by stereoelectronic effects. While the electronic effects of the acid-containing chains in **25w** and **40** are strikingly opposite in nature, they share in common an electronic interaction with the aryl ring. This presumably provides a favorable conformational bias and results in a significant entropic advantage not available to the propionic acid derivative **41**.

The effects of structural modification of the tether between the phenoxy and heterocyclic rings were also evaluated and revealed some sensitivity to variations within this region. Replacement of the CH_2 β to the oxazole ring of **40** gave an ether (**45**) that is 10-fold weaker, a structure–activity correlate also reflected in the paired propionates **46** and **41**. However, the detrimental effects of this modification are confined to the propionate/propenoate series since the bis-ether **49**, which contains the oxyacetic acid side chain, is as potent as the progenitor **25w**. The single thioether derivative examined, **52**, is almost 1 order of magnitude weaker than **25w** as a platelet aggregation inhibitor.

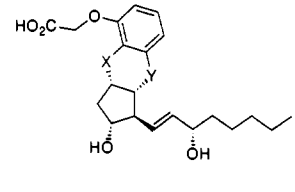
The final aspect of SAR examined using the acid **25w** as a template focused on structural variations associated with the carboxylic acid terminus. Biological activity is sensitive to the level of substitution α to the carboxylic acid moiety since the introduction of one (**25ac**) or two (**25ad**) methyl groups leads to a progressive reduction in potency. However, replacement of the carboxylate terminus with a tetrazole moiety provided a compound, **53**, equipotent with **25w**, demonstrating that the tetrazole ring functions as an effective carboxylic acid isostere in this PGI_2 mimetic. A similar observation was made with the alkane-substituted pyrazole series studied earlier.[23]

The incorporation of an aromatic ring directly adjacent to the carboxy terminus was not well-tolerated. The only benzoic acid derivative that demonstrates significant inhibition of platelet aggregation is the para-substituted compound **57c**, but this compound is over 1 order of magnitude weaker than the simpler nonanoate **18b**. The poor activity recorded for this series is perhaps somewhat surprising in view of the fact that taprostene (**7**) and related compounds[19a] are effective PGI_2 mimetics, demonstrating tolerance of a benzoic acid terminus in the appropriate setting. This observation may be indicative of subtle differences in the mode of binding of the two structurally distinct classes of PGI_2 mimetic.

The strategy of systematically equating the effects of side-chain rigidification with potency for this series of nonprostanoid PGI_2 mimetic has led to a deeper understanding of this class of platelet aggregation inhibitor. In addition to refining the proposed topological description of the pharmacophore, the structure–activity variations reported herein provide some insight into the important topographical relationships between the key structural elements. It is apparent that potency is highly sensitive to the location of the phenyl ring within the side chain, the pattern of substitution, and the identity of the concatenating atoms. The optimal side-chain configuration to emerge from this study is the *m*-phenoxyacetic acid moiety attached to the heterocycle through a two-atom tether. Interestingly, this side chain has previously been incorporated successfully into prostanoid-based ligands for the PGI_2 receptor. The PGE_1 analogue **58** is 1 order of



58



59a, X = Y = CH_2
59b, X = O, Y = CH_2
59c, X = Y = O

magnitude more potent than PGE_1 as an inhibitor of ADP-induced aggregation of human platelets.[51] Integration of the *m*-phenoxyacetic acid moiety into a tricyclic ring system structurally analogous to PGI_2 provided effective and stable mimetics (**59**) that established the bound conformation of PGI_2 to more closely resemble a Z rather than an L shape.[52,53] Although the relationship between

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the nonprostanoid PGI_2 mimetic pharmacophore and that defined by compounds patterned more closely after the natural ligand remains obscure, the structural homologies between **37** and **58a** provide a foundation for speculation. If one assumes a high degree of overlap of the phenoxy ring and carboxylate terminus of **37** and **58a** and a conformation of **37** resembling that depicted in Figure 4, the diphenyloxazole moiety reasonably defines two regions of the PGI_2 receptor. More extensive structural overlap between the two classes of PGI_2 agonist suggests analogy between the π system of the heterocycle of **37** and the C_{13}–C_{14} double bond of **58a**. This conformation places the two phenyl rings of **37** in the domain occupied by the β side chain of **58a**, a region of the PGI_2 molecule that has been shown to tolerate quite wide structural variation.[13] Some adjustment of this arrangement would allow the heteroatoms of the oxazole ring of **37** to effectively mimic the hydrogen-bond-accepting properties of the C-11 (PGI_2 numbering) hydroxyl group of **58a**. However, there is no evidence to suggest that the heterocyclic ring in nonprostanoid PGI_2 mimetics functions other than as a scaffold on which to arrange the pharmacophoric elements, since activity is relatively insensitive to the identity of this ring.[23,54] Alternatively, the diphenyloxazole moiety may occupy a hydrophobic cavity of the PGI_2 receptor that is largely ignored by the natural ligand and its close analogues. Regardless of the mode of binding, it is clear that the relatively simple combination of a carboxylic acid functionality appropriately configured with a di- or triphenylated ring system,[21-23] or its structural equivalent,[20] is capable of eliciting the conformational changes in PGI_2 receptor structure that are responsible for signal transduction to the G-protein that provides the link between this receptor and adenylate cyclase.

Although the compounds described in this report are potent PGI_2 mimetics at the biochemical level, effectively displacing [^{3}H]iloprost from platelet membranes and stimulating adenylate cyclase, in PRP they are generally weaker inhibitors of platelet function. This is most likely due to the higher affinity of these lipophilic compounds for plasma proteins than PGI_2 or its structurally similar analogues.[49] Nevertheless, the *cis*-olefin **37** is only 20- and 70-fold less potent than PGI_2 and iloprost, respectively, which compares quite favorably with the efficacy reported for many PGI_2 mimetics that are as complex as the natural ligand.[13] The acid **25w** is 2–3 orders of magnitude less effective in PRP than PGI_2 and iloprost but offers the distinct advantage of excellent oral bioavailability and an extended duration of action in vivo. Following oral administration of a 20 mg/kg dose to rats, BMY 42393 exhibited significant inhibition of platelet function, measured 20 h postdose using a heterologous ex-vivo aggregometry protocol.[49,55] The biochemical and pharmacological properties of **25w** (BMY 42393) have been examined in some detail and this compound has been characterized as an effective and potent, orally active antithrombotic agent in two different animal models.[49]

In summary, we have demonstrated that the 4,5-diphenyloxazole moiety is an effective platform on which to build PGI_2 mimetics and that structural variation in the acid-containing side chain exerts a significant influence on biological activity. The structure–activity relationships developed for this series have allowed some refinement of the topological and topographical features of the nonprostanoid PGI_2 mimetic pharmacophore developed from an earlier study. The most potent platelet aggregation inhibitors to be identified from this study incorporate a *m*-phenoxyacetic acid side chain attached to the heterocycle through a two-atom tether, a side chain that appears to be of general value in this type of PGI_2 mimetic.[54]

Experimental Section

Melting points were recorded on a Thomas-Hoover capillary apparatus and are uncorrected. Proton (^{1}H NMR) magnetic resonance spectra were recorded on a either a Bruker AM or a Varian Gemini FT instrument operating at 300 MHz. All spectra were recorded using tetramethylsilane as an internal standard and signal multiplicity was designated according to the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, bs = broad singlet. Infrared (IR) spectra were obtained using a Perkin-Elmer 1800 FT IR, scanning from 4000 to 400 cm^{-1} and calibrated to the 1601-cm^{-1} absorption of a polystyrene film. Mass spectra data were obtained on a Finnigan Model 4500 GC/MS using electrical or chemical ionization (isobutane) procedures. Fast atom bombardment (FAB) mass spectra were obtained on a Kratos MS 25 spectrometer using *m*-nitrobenzyl alcohol (NOBA) as the matrix. Analytical samples were dried in vacuo at 78 °C or in the presence of P_2O_5 at room temperature for at least 12 h. Elemental analyses were provided by Bristol-Myers Squibb's Analytical Chemistry Department or Oneida Research Services, Whitesboro, NY. Unless otherwise stated, an extractive workup procedure comprised extraction of the aqueous layer with solvent (three times), washing the combined extracts with H_2O (usually a single time except where DMF was present when the organic phase was washed three times) and drying over Na_2SO_4 or $MgSO_4$ prior to evaporation of the solvent in vacuo.

2-Oxo-1,2-diphenylethyl 8-Bromooctanoate. A mixture of **13** (10.00 g, 47 mmol), 8-bromooctanoic acid (11.57 g, 52 mmol), 1,3-dicyclohexylcarbodiimide (11.66 g, 57 mmol), DMAP (catalytic amount), and CH_2Cl_2 (250 mL) was stirred at room temperature under an atmosphere of N_2. After 17 h, the mixture was filtered and concentrated to leave an oil which was chromatographed on a column of silica gel. Elution with a mixture of hexane and Et_2O (9:1) afforded 2-oxo-1,2-diphenylethyl 8-bromooctanoate (18.43 g, 93%): mp 58–62 °C; IR (KBr) 1730, 1700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.20–1.45 (6 H, m, C*H*$_2$), 1.67 (2 H, quintet, J = 7 Hz, C*H*$_2$), 1.82 (2 H, quintet, J = 7 Hz, C*H*$_2$), 2.46 (2 H, m, C*H*$_2$CO$_2$R), 3.37 (2 H, t, J = 7 Hz, C*H*$_2$Br), 6.86 (1 H, s, C*H*OR), 7.30–7.55 (8 H, m, aryl *H*), 7.92 (2 H, d, J = 7.5 Hz, aryl *H* ortho to C=O); MS m/z 417 (M^+). Anal. ($C_{22}H_{25}BrO_3$) C, H, N.

2-(7-Bromoheptyl)-4,5-diphenyloxazole (15). A solution of 2-oxo-1,2-diphenylethyl 8-bromooctanoate (16.00 g, 38 mmol) and NH_4OAc (14.77 g, 192 mmol) in AcOH (240 mL) was heated at reflux. After 1 h, the mixture was poured onto H_2O and extracted with CH_2Cl_2 to leave an oil. Chromatography on a column of silica gel using a mixture of hexane and Et_2O (9:1) as eluent afforded **15** (13.20 g, 86%). A sample was rechromatographed under identical conditions to provide an analytically pure sample as an oil: IR (film) 1605, 1600, 1505, 1450 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.30–1.60 (6 H, m, C*H*$_2$), 1.80–1.95 (4 H, m, C*H*$_2$), 2.84 (2 H, t, J = 7.5 Hz, C*H*$_2$-oxazole), 3.38 (2 H, t, J = 7 Hz, C*H*$_2$Br), 7.20–7.40 (6 H, m, aryl *H*), 7.50–7.80 (4 H, m, aryl *H*); MS m/z 398 (M^+). Anal. ($C_{22}H_{24}BrNO$) C, H, N.

Dimethyl 2-[7-(4,5-Diphenyl-2-oxazolyl)heptyl]propanedioate (16). A mixture of **15** (10.00 g, 25 mmol), dimethyl malonate (9.95 g, 8.60 mL, 75 mmol), potassium *tert*-butoxide (8.44 g, 75 mmol), 18-crown-6 (catalytic amount), and THF (200 mL) was heated to reflux under an atmosphere of N_2. After 17.5 h, the mixture was cooled, diluted with 2 N HCl solution, and

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(54) Meanwell, N. A.; Rosenfeld, M. J.; Trehan, A. K.; Romine, J. L.; Wright, J. J. K.; Brassard, C. L.; Buchanan, J. O.; Federici, M. E.; Fleming, J. S.; Gamberdella, M.; Zavoico, G. B.; Seiler, S. M. Nonprostanoid Prostacyclin Mimetics. 3. Structural Variations of the Diphenyl Heterocycle Moiety. *J. Med. Chem.*, following paper in this issue.
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extracted with CH_2Cl_2 to leave an oil. Chromatography on a column of silica gel using a mixture of hexane and Et_2O (9:1) as eluent afforded **16** (9.47 g, 83%) as an oil: IR (film) 1760, 1740 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20–1.50 (8 H, m, CH_2), 1.70–1.90 (4 H, m, CH_2), 2.80 (2 H, t, J = 7.5 Hz, CH_2-oxazole), 3.33 (1 H, t, J = 7.5 Hz, CH_2-oxazole), 3.33 (1 H, t, J = 7.5 Hz, $CH(CO_2Me)_2$), 3.68 (6 H, s, CO_2CH_3), 7.20–7.40 (6 H, m, aryl H), 7.50–7.70 (4 H, m, aryl H); MS m/z 450 (MH^+). Anal. ($C_{27}H_{31}NO_5 \cdot 0.1H_2O$) C, H, N.

2-[7-(4,5-Diphenyl-2-oxazolyl)heptyl]propanedioic Acid (17). A mixture of **16** (6.00 g, 13 mmol), 5 N NaOH solution (13.4 mL), H_2O (120 mL), and MeOH (20 mL) was stirred at room temperature. After 10 min, the mixture was heated to reflux for 1 h before adding H_2O (80 mL) and 5 N NaOH solution (13 mL). After heating at reflux for 3 h, the mixture was cooled, acidified with 2 N HCl solution, and extracted with Et_2O to give **17** (5.65 g, 100%): mp 115–117 °C (CH_2Cl_2/Et_2O/hexane); IR (KBr) 1720 (CO_2H) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.10–1.45 (8 H, m, CH_2), 1.60–1.85 (4 H, m, CH_2), 2.78 (2 H, t, J = 7.5 Hz, CH_2-oxazole), 3.18 (1 H, t, J = 7.5 Hz, $CH(CO_2H)_2$), 7.25–7.50 (6 H, m, aryl H), 7.50–7.60 (4 H, m, aryl H), 12.64 (2 H, bs, CO_2H); MS m/z 422 (MH^+), 378 ($MH^+ - CO_2$). Anal. ($C_{25}H_{27}NO_5$) C, H, N.

4,5-Diphenyl-2-oxazolenonanoic Acid (18b). Acid **17** (4.50 g, 10 mmol) was stirred at 150 °C for 2 h, cooled, and triturated with a mixture of hexane and Et_2O (1:1) to give a white solid. Recrystallization from ^{i}PrOH/H_2O afforded **18b** (3.15 g, 87%): mp 83–85 °C; IR (KBr) 1730 (CO_2H) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.10–1.40 (8 H, m, CH_2), 1.46 (2 H, m, CH_2), 1.71 (2 H, m, CH_2), 2.15 (2 H, t, J = 7 Hz, CH_2CO_2H), 2.76 (2 H, t, J = 7 Hz, CH_2-oxazole), 7.20–7.45 (6 H, m, aryl H), 7.45–7.65 (4 H, m, aryl H), 11.99 (1 H, bs, CO_2H); MS m/z 378 (MH^+). Anal. ($C_{24}H_{27}NO_3$) C, H, N.

Methyl 4,5-Diphenyl-2-oxazoleoctanoate (19d). A mixture of **13** (6.00 g, 28 mmol), azelaic acid monomethyl ester (7.17 g of 92% pure material, 32 mmol), 1,3-dicyclohexylcarbodiimide (7.00 g, 34 mmol), DMAP (catalytic amount), and CH_2Cl_2 (120 mL) was stirred at room temperature. After 16 h, the mixture was filtered, the sovlent was evaporated, and NH_4OAc (10.90 g, 141 mmol) and AcOH (150 mL) were added. The mixture was heated at reflux for 65 min, cooled, diluted with H_2O, and extracted with Et_2O. The residual oil was chromatographed on a column of silica gel using a mixture of hexane and Et_2O (7:3) as eluent to give **19d** (8.24 g, 77%) as an oil: IR (film) 1745 (CO_2CH_3) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10–1.35 (6 H, m, CH_2), 1.45 (2 H, quintet, J = 7 Hz, CH_2), 1.67 (2 H, quintet, J = 7 Hz, CH_2), 2.12 (2 H, t, J = 7.5 Hz, $CH_2CO_2CH_3$), 2.66 (2 H, t, J = 7.5 Hz, CH_2-oxazole), 3.47 (3 H, s, CO_2CH_3), 7.05–7.25 (6 H, m, aryl H), 7.35–7.55 (4 H, m, aryl H); MS m/z 378 (MH^+). Anal. ($C_{24}H_{27}NO_3$) C, H, N.

4,5-Diphenyl-2-oxazoleoctanoic Acid (18d). A sample of **19d** (7.00 g, 18.5 mmol) was hydrolyzed under conditions analogous to that described for **17** to give **18d** (5.25 g, 77%): mp 70–73 °C (Et_2O/CH_2Cl_2/hexane); IR (KBr) 1720 (CO_2H) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20–1.45 (6 H, m, CH_2), 1.54 (2 H, quintet, J = 7 Hz, CH_2), 1.75 (2 H, quintet, J = 7 Hz, CH_2), 2.23 (2 H, t, J = 7.5 Hz, CH_2CO_2H), 2.76 (2 H, t, J = 7.5 Hz, CH_2-oxazole), 7.10–7.35 (6 H, m, aryl H) 7.40–7.60 (4 H, m, aryl H), 11.74 (1 H, bs, CO_2H); MS m/z 364 (MH^+). Anal. ($C_{23}H_{25}NO_3$) C, H, N.

4,5-Diphenyl-2-oxazolehexanoic Acid (18e). Using the procedure described for the preparation of **19d**, a mixture of **13** (5.00 g, 23 mmol) and suberic acid (12.31 g, 71 mmol) was coupled using DCC (5.83 g, 28 mmol) and the crude material subjected to oxazole ring formation. Extraction with CH_2Cl_2 gave an oil which was chromatographed on a column of silica gel. Elution with a mixture of hexane and Et_2O (3:2) afforded 2,2′-(1,6-hexanediyl)bis(4,5-diphenyloxazole) (**20e**) (1.50 g): mp 152–154 °C (CH_2Cl_2/hexane); IR (KBr) 2980, 1750, 1620, 1600, 1590, 1580, 1520 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.54 (4 H, m, CH_2), 1.90 (4 H, m, CH_2), 2.87 (4 H, t, J = 6 Hz, CH_2-oxazole), 7.20–7.50 (12 H, m, aryl H), 7.58 (4 H, d, J = 6 Hz, aryl H), 7.65 (4 H, d, J = 6 Hz, aryl H); MS m/z 525 (MH^+). Anal. ($C_{36}H_{32}N_2O_2$).

Further elution afforded **18e** (3.85 g, 46%): mp 91–93 °C (Et_2O/hexane); IR (KBr) 2960, 1740 (CO_2H) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.32 (4 H, m, CH_2), 1.50 (2 H, quintet, J = 7 Hz, CH_2), 1.72 (2 H, quintet, J = 7 Hz, CH_2), 2.19 (2 H, t, J = 6 Hz, CH_2CO_2H), 2.76 (2 H, t, J = 6 Hz, CH_2-oxazole), 7.20–7.45 (6 H, m, aryl H), 7.49 (2 H, d, J = 6 Hz, aryl H), 7.56 (2 H, d, J = 6 Hz, aryl H), 12.05 (1 H, s, CO_2H); MS m/z 350 (MH^+). Anal. ($C_{22}H_{23}NO_3$) C, H, N.

Ethyl 4-[4-(4,5-Diphenyl-2-oxazolyl)phenoxy]butanoate (24a). Na metal (1.16 g, 0.05 g-atom) was dissolved in EtOH (180 mL), and 4-(4-ethoxy-4-oxobutoxy)benzoic acid (10.67 g, 42 mmol) added. After 15 min, concentrated H_2SO_4 (4 drops) and **21** (11.64 g, 42 mmol) were added, and the mixture was heated at reflux. After 2.25 h, the mixture was cooled, diluted with H_2O, and extracted with CH_2Cl_2 to leave an oil. This was dissolved in AcOH (100 mL), NH_4OAc (16.30 g, 210 mmol) added, and the mixture heated to reflux. After 1 h, the mixture was cooled, diluted with H_2O, and extracted with CH_2Cl_2 to leave an oil that crystallized upon trituration with hexanes. Recrystallization from ^{i}PrOH furnished **24a** (5.55 g, 30%): mp 90–92 °C; IR (KBr) 1740 (CO_2Et) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.41 (3 H, t, J = 7 Hz, $CO_2CH_2CH_3$), 2.28 (2 H, quintet, J = 7 Hz, CH_2CH_2), 2.68 (2 H, t, J = 7 Hz, CH_2CO_2Et), 4.21 (2 H, t, J = 7 Hz, OCH_2CH_2), 4.30 (2 H, q, J = 7 Hz, OCH_2CH_3), 7.11 (2 H, d, J = 8 Hz, aryl H), 7.40–7.60 (6 H, m, aryl H), 7.70–7.90 (4 H, m, aryl 1 H), 8.22 (2 H, d, J = 8 Hz, aryl H meta to O); MS m/z 428 (MH^+). Anal. ($C_{27}H_{25}NO_4$) C, H, N.

4-[4-(4,5-Diphenyl-2-oxazolyl)phenoxy]butanoic Acid (25a). A sample of **24a** (3.55 g, 8 mmol) was hydrolyzed under conditions analogous to that described for **17** to give **25a** (1.62 g, 50%): mp 163–165 °C (^{i}PrOH); IR (KBr) 1750, 1710 (CO_2H) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.96 (2 H, quintet, J = 7 Hz, CH_2CH_2O), 2.40 (2 H, t, J = 7 Hz, CH_2CO_2H), 4.04 (2 H, t, J = 7 Hz, O-CH_2), 7.06 (2 H, d, J = 8.5 Hz, aryl H ortho to O), 7.30–7.50 (6 H, m, aryl H), 7.55–7.70 (4 H, m, aryl H), 7.98 (2 H, d, J = 8.5 Hz, aryl H meta to O), 12.19 (1 H, s, CO_2H); MS m/z 400 (MH^+). Anal. ($C_{25}H_{21}NO_4$) C, H, N.

3-(4,5-Diphenyl-2-oxazolyl)phenol. A procedure similar to that described for the preparation of **24a** using Na metal (3.01 g, 0.13 g atom), EtOH (250 mL), 3-hydroxybenzoic acid (15.05 g, 110 mmol), concentrated H_2SO_4 (6 drops), and **21** (30.00 g, 110 mmol) was employed to prepare the ester. Heating the crude material in AcOH (250 mL) with NH_4OAc (42.00 g, 550 mmol) furnished 3-(4,5-diphenyl-2-oxazolyl)phenol (11.70 g, 33%): mp 154–156 °C after chromatograpy on a column of silica gel (hexane/Et_2O 3:1 as eluent); IR (KBr) 3400, 1740, 1640, 1600 cm^{-1}; ^1H NMR (DMSO-d_6) δ 6.92 (1 H, dd, J = 9 Hz, J' = 2 Hz, aryl H ortho to OH), 7.25–7.70 (13 H, m, aryl H); MS m/z 314 (MH^+). Anal. ($C_{21}H_{15}NO_2$) C, H, N.

Ethyl 5-[3-(4,5-Diphenyl-2-oxazolyl)phenoxy]pentanoate (24c). A mixture of 3-(4,5-diphenyl-2-oxazolyl)phenol (4.00 g, 13 mmol), ethyl 5-bromovalerate (2.90 g, 2.20 mL, 14 mmol), K_2CO_3 (2.10 g, 16 mmol), KI (catalytic amount), and DMF (40 mL) was stirred at 110 °C. After 20 min, the mixture was cooled, combined with a mixture containing 25% of the above, previously treated in an identical manner, and poured onto H_2O. The mixture was extracted with Et_2O and the residual oil chromatographed on a column of silica gel. Elution with a mixture of hexane and Et_2O (2:1) gave **24c** (5.19 g, 74%): mp 64–66 °C; IR (KBr) 1740 (CO_2Et) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.17 (3 H, t, J = 7 Hz, OCH_2CH_3), 1.73 (4 H, m, CH_2), 2.31 (2 H, t, J = 7 Hz, CH_2CO_2Et), 3.97 (2 H, t, J = 6 Hz, OCH_2), 4.04 (2 H, t, J = 7 Hz, OCH_2CH_3), 6.89 (1 H, dd, J = 8 Hz, J' = 2 Hz, aryl H ortho to O), 7.20–7.40 (7 H, aryl H), 7.50–7.75 (6 H, m, aryl H); MS m/z 442 (MH^+). Anal. ($C_{28}H_{27}NO_4$) C, H, N.

5-[3-(4,5-Diphenyl-2-oxazolyl)phenoxy]pentanoic Acid (25c). Hydrolysis of a sample of **24c** (4.00 g, 9 mmol) as described for **17** gave **25c** (2.95 g, 78%): mp 111–113 °C (CH_2Cl_2/hexane); IR (KBr) 1740, 1720 (CO_2H) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.87 (4 H, m, CH_2), 2.46 (2 H, t, J = 6.5 Hz, CH_2CO_2H), 4.06 (2 H, t, J = 5 Hz, OCH_2), 6.98 (1 H, dd, J = 7.5 Hz, J' = 2.5 Hz, aryl H ortho to O), 7.30–7.50 (7 H, m, aryl H), 7.60–7.80 (6 H, m, aryl H), 11.71 (1 H, bs, CO_2H); MS m/z 414 (MH^+). Anal. ($C_{26}H_{23}NO_4$) C, H, N.

3-[2-(4,5-Diphenyl-2-oxazolyl)ethenyl]phenol. Alkylation of 3-hydroxycinnamic acid (10.00 g, 58 mmol) with **21** (16.76 g, 58 mmol) followed by oxazole ring formation was accomplished as described for the preparation of **24a**. Trituration of the resultant khaki solid with Et_2O gave 3-[2-(4,5-diphenyl-2-oxazolyl)ethenyl]phenol (10.80 g, 52%): mp 201–203 °C (EtOH); IR (KBr) 3400, 1740, 1640, 1600 cm^{-1}; ^1H NMR (DMSO-d_6) δ 6.77 (1 H, d, J = 7.5 Hz, aryl H), 7.00–7.35 (4 H, m, aryl H + 1 olefinic

H), 7.35–7.50 (6 H, m, aryl *H*), 7.53 (1 H, d, *J* = 16 Hz, olefinic *H*), 7.60–7.70 (4 H, m, aryl *H*), 9.58 (1 H, s, O*H*); MS *m/z* 340 (MH^+). Anal. ($C_{23}H_{17}NO_2$) C, H, N.

Methyl [3-[2-(4,5-Diphenyl-2-oxazolyl)ethenyl]phenoxy]acetate (24p). A mixture of 3-[2-(4,5-diphenyl-2-oxazolyl)ethenyl]phenol (31.80 g, 94 mmol), methyl bromoacetate (14.95 g, 9.23 mL, 98 mmol), K_2CO_3 (14.70 g, 100 mmol), KI (catalytic amount), and CH_3CN (500 mL) was heated at reflux for 1 h. The mixture was filtered and concentrated to give **24p** (38.55 g, 100%). An analytical sample was obtained by chromatographing a portion on a column of silica gel using a mixture of hexane and Et_2O (3:2) as eluent followed by recrystallization from Et_2O: mp 79–82 °C; IR (KBr) 1765, 1740 (CO_2Me) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (1.25 H, t, *J* = 7 Hz, OCH_2CH_3 from Et_2O), 3.53 (0.75 H, q, *J* = 7 Hz, OCH_2CH_3 from Et_2O), 3.88 (3 H, s, OCH_3), 4.73 (2 H, s, OCH_2), 6.94 (1 H, dd, *J* = 7.5 Hz, *J'* = 2 Hz, aryl *H* ortho to O), 7.06 (1 H, d, *J* = 16 Hz, olefinic *H*), 7.14 (1 H, t, *J* = 2 Hz, aryl *H* ortho to O and olefin), 7.20–7.55 (8 H, m, aryl *H*), 7.60 (1 H, d, *J* = 16 Hz, olefinic *H*), 7.70–7.90 (5 H, m, aryl *H*); MS *m/z* 412 (MH^+). Anal. ($C_{26}H_{21}NO_4 \cdot 0.3Et_2O$) C, H, N.

[3-[2-(4,5-Diphenyl-2-oxazolyl)ethenyl]phenoxy]acetic Acid (25p). A mixture of **24p** (1.00 g, 2.5 mmol), 5 N NaOH solution (2 mL), and MeOH (15 mL) was heated on a steam bath for 10 min, concentrated in vacuo, and diluted with H_2O and 2 N HCl solution. The yellow solid was combined with the crude product from a reaction performed on 1.46 g of ester using 3 mL of 5 N NaOH in 40 mL of MeOH and recrystallized from EtOH to give **25p** (1.70 g, 70%): mp 213–215 °C; IR (KBr) 1745 (CO_2H) cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.75 (2 H, s, OCH_2), 6.90 (1 H, m, aryl *H*), 7.20–7.70 (13 H, m, aryl *H* and olefinic *H*), 13.02 (1 H, bs, CO_2H); MS *m/z* 398 (MH^+). Anal. ($C_{25}H_{19}NO_4$) C, H, N.

3-[3-Hydroxyphenyl]propionic Acid. A solution of 3-hydroxycinnamic acid (20.00 g, 0.12 mmol) in MeOH (200 mL) was hydrogenated over 10% Pd on C (1.25 g) at 45–50 psi using a Parr hydrogenation apparatus. After 4 h, the mixture was filtered through Celite and the solvent evaporated to leave a tan solid which was used without further purification: ^1H NMR (CD_3OD) δ 2.32 (2 H, t, *J* = 7.5 Hz, CH_2CO_2H), 2.68 (2 H, t, *J* = 7.5 Hz, CH_2Ar), 6.30–6.50 (3 H, m, aryl *H* ortho and para to OH), 6.82 (1 H, t, *J* = 8.5 Hz, aryl *H* meta to OH); MS *m/z* 166 (MH^+).

3-[2-(4,5-Diphenyl-2-oxazolyl)ethyl]phenol (22a). Alkylation of 3-(3-hydroxyphenyl)propionic acid (19.38 g, 0.12 mol) with **21** (32.11 g, 0.12 mol) and subsequent oxazole ring formation was accomplished under conditions described for the preparation of **24a** to afford **22a** (29.35 g, 73%): mp 146–147.5 °C (hexane/CH_2Cl_2 2:1); IR (KBr) 3200, 1610, 1580, 1460 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.05 (4 H, m, CH_2CH_2-oxazole), 6.60 (2 H, m, aryl *H* of phenol ring), 6.68 (1 H, d, *J* = 7.5 Hz, aryl *H*), 7.05 (1 H, t, *J* = 7.5 Hz, aryl *H* meta to OH), 7.20–7.45 (6 H, m, aryl *H*), 7.50–7.80 (5 H, m, aryl *H* + O*H*); MS *m/z* 342 (MH^+). Anal. ($C_{23}H_{19}NO_2 \cdot 0.05H_2O$) C, H, N.

Methyl [3-[2-(4,5-Diphenyl-2-oxazolyl)ethyl]phenoxy]acetate (24w). Alkylation of 3-[2-(4,5-diphenyl-2-oxazolyl)-ethyl]phenol (3.41 g, 10 mmol) with methyl bromoacetate according to the procedure described for the preparation of **24p** gave **24w** (3.59 g, 86%) as a viscous oil after chromatography over silica gel using a mixture of hexane, EtOAc, and Et_3N (75:25:1) as eluent: IR (film) 1760, 1740 (CO_2CH_3), 1610, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.14 (4 H, s, CH_2CH_2-oxazole), 3.76 (3 H, s, CO_2CH_3), 4.60 (2 H, s, OCH_2), 6.75 (1 H, dd, *J* = 8 Hz, *J'* = 2.5 Hz, aromatic *H* ortho to O), 6.90 (1 H, d, *J* = 8 Hz, aromatic *H* para to O), 7.15–7.40 (7 H, m, aromatic *H*), 7.50–7.75 (4 H, m, aromatic *H*); MS *m/z* 414 (MH^+). Anal. ($C_{26}H_{23}NO_4$) C, H, N.

[3-[2-(4,5-Diphenyl-2-oxazolyl)ethyl]phenoxy]acetic Acid (25w). Saponification of **24w** (2.25 g, 5.5 mmol) as described for **17** gave **25w** (1.74 g, 80%): mp 153.3–154.5 °C (recrystallized twice from hexane/CH_2Cl_2 2:1); IR (KBr) 1750, 1720 (CO_2H), 1605, 1590 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.12 (4 H, m, CH_2CH_2-oxazole), 4.64 (2 H, s, OCH_2), 6.73 (1 H, dd, *J* = 8 Hz, *J'* = 2 Hz, aromatic *H* ortho to O), 6.88 (2 H, m, aromatic *H* ortho and para to O), 7.20 (1 H, t, *J* = 8 Hz, aromatic *H* meta to O), 7.30–7.50 (6 H, m, aromatic *H*), 12.98 (1 H, bs, CO_2H); MS *m/z* 400 (MH^+). Anal. ($C_{25}H_{21}NO_4$) C, H, N.

1-[3-[(1,1-Dimethylethyl)dimethylsiloxy]phenyl]-2-(4,5-diphenyl-2-oxazolyl)ethanone (31). Oxazole **29** (5.00 g, 21 mmol) in dry THF (60 mL) was added dropwise to a solution of LDA (4.83 g, 46 mmol) in dry THF (60 mL) maintained at −78 °C under an atmosphere of N_2. The mixture was stirred for 30 min and then a solution of **30** (5.70 g, 21 mmol) in dry THF (30 mL) added dropwise. After stirring for 1.5 h, the mixture was poured onto saturated NH_4Cl solution and extracted with CH_2Cl_2 to give an oil. Chromatography on a column of silica gel using a mixture of hexane and EtOAc (9:1) as eluent gave **31** (8.71 g, 87%). ^1H NMR ($CDCl_3$) δ 0.20 and 0.24 (6 H, s, $Si(CH_3)$), 0.98 and 1.01 (9 H, s, $C(CH_3)_3$), 4.51 (1.46 H, s, CH_2CO), 6.12 (0.54 H, s, C*H*=COH), 6.88 and 7.05 (1 H, dd, *J* = 8 Hz, *J'* = 1.5 Hz, aromatic *H*), 7.20–7.70 (13 H, m, aromatic *H*); MS *m/z* 470 (MH^+).

3-[2-(4,5-Diphenyl-2-oxazolyl)ethynyl]phenol (33). A solution of **31** (20.44 g, 43 mmol) and 2-chloro-3-ethylbenzoxazolium tetrafluoroborate (14.4 g, 53 mmol) in CH_2Cl_2 (63 mL) was cooled to 0 °C and Et_3N (34.34 g, 47.2 mL, 0.34 mol) added dropwise. The mixture was warmed to room temperature and stirred for 17 h before the solvent was evaporated. The residue was diluted with H_2O and extracted with Et_2O to give an oil which was dissolved in dry THF (200 mL). A solution of $^nBu_4NF$ (8.35 g, 32 mmol) in THF (32 mL) was added dropwise and the mixture stirred at room temperature for 30 min. HCl (1 N) solution was added and the mixture extracted with Et_2O to give an oil which was chromatographed on a column of silica gel using a mixture of hexane and Et_2O (9:1 to 1:1 gradient) as eluent to afford **33** (8.70 g, 58%): IR (film) 3200, 2230, 1600 cm^{-1}; ^1H NMR (DMSO-d_6) δ 6.92 (1 H, dd, *J* = 8 Hz, *J'* = 2 Hz), 7.02 (1 H, d, *J* = 2 Hz), 7.12 (1 H, d, *J* = 8 Hz), 7.28 (1 H, t, *J* = 8 Hz), 7.38–7.50 (6 H, m), 7.52–7.75 (4 H, m), 9.94 (1 H, s, O*H*); MS *m/z* 338 (MH^+). Anal. ($C_{23}H_{15}NO_2 \cdot 0.2H_2O$) C, H, N.

Methyl [3-[2-(4,5-Diphenyl-2-oxazolyl)ethynyl]phenoxy]acetate (34). A sample of **33** (1.05 g, 3 mmol) was alkylated with methyl bromoacetate under conditions described for the preparation of **24p** to give **34** (0.80 g, 63%) after chromatography on a column of silica gel [hexane and EtOAc (4:1)]: IR (film) 2230, 1760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.82 (3 H, s, CO_2CH_3), 4.66 (2 H, s, OCH_2), 7.00 (1 H, d, *J* = 8 Hz, *J'* = 2 Hz), 7.11 (1 H, d, *J* = 2 Hz), 7.20–7.45 (8 H, m), 7.60–7.70 (4 H, m); MS *m/z* 410 (MH^+). Anal. ($C_{26}H_{19}NO_4$) C, H, N.

[3-[2-(4,5-Diphenyl-2-oxazolyl)ethynyl]phenoxy]acetic Acid (35). A mixture of **34** (0.62 g, 1.5 mmol), $LiOH \cdot H_2O$ (0.13 g, 3 mmol), MeOH (10 mL), and H_2O (1 mL) was heated at reflux for 40 min. The solution was concentrated in vacuo, diluted with H_2O and 1 N HCl solution and extracted with CH_2Cl_2 to give a solid. Recrystallization from EtOAc and hexane gave **35** (0.33 g, 55%): mp 164 °C; IR (KBr) 2230, 1745 cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.74 (2 H, s, OCH_2), 7.10 (1 H, dd, *J* = 8 Hz, *J'* = 2 Hz), 7.23 (1 H, s), 7.25–7.50 (8 H, m), 7.50–7.65 (4 H, m); MS *m/z* 396 (MH^+). Anal. ($C_{25}H_{17}NO_4$) C, H, N.

***cis*-Methyl [3-[2-(4,5-Diphenyl-2-oxazolyl)ethenyl]phenoxy]acetate (36).** A solution of **34** (0.50 g, 1.5 mmol) and quinoline (5 drops) in MeOH (75 mL) was hydrogenated over 5% Pd on C (catalytic amount) at atmospheric pressure. After 3 h, the MeOH was evaporated, and the residue diluted with CH_2Cl_2 and washed with ice-cold 0.5 N HCl solution. The organic phase was dried over Na_2SO_4 and concentrated to leave an oil. Chromatography on a column of silica gel using a mixture of hexane, EtOAc, and Et_3N (18:1:1) afforded **36** (0.11 g, 28%): IR (film) 1760, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.75 (3 H, s, CO_2CH_3), 4.62 (2 H, s, OCH_2), 6.50 (1 H, d, *J* = 12.9 Hz, olefinic *H*), 6.88 (1 H, dd, *J* = 12.9 Hz, olefinic *H*), 6.94 (1 H, dd, *J* = 8 Hz, *J'* = 2 Hz, aromatic *H*), 7.25–7.50 (11 H, m), 7.65–7.70 (3 H, m); MS *m/z* 412 (MH^+). Anal. ($C_{26}H_{21}NO_4$) C, H, N.

***cis*-[3-[2-(4,5-Diphenyl-2-oxazolyl)ethenyl]phenoxy]acetic Acid, Sodium Salt (37).** A mixture of **36** (0.12 g, 0.3 mmol), 1 N NaOH solution (0.29 mL, 0.3 mmol), and MeOH (5 mL) was stirred at room temperature for 66 h. The solvent was evaporated and the residue triturated with Et_2O and filtered to give **37** (0.06 g, 50%): mp indistinct; IR (KBr) 1610, 1425 cm^{-1}; ^1H NMR (D_2O) δ 4.14 (2 H, s, OCH_2), 6.05 (1 H, d, *J* = 12.8 Hz, olefinic *H*), 6.43 (3 H, m), 6.60–6.70 (4 H, m), 6.80–7.01 (8 H, m); MS (FAB) *m/z* 442 (M^+ + Na), 422 (MH^+). Anal. ($C_{25}H_{18}NO_4Na \cdot 1.45H_2O$) C, H, N.

3-[2-(4,5-Diphenyl-2-oxazolyl)ethyl]phenyl Trifluoromethanesulfonate (38). Trifluoromethanesulfonic anhydride (16.55 g, 58 mmol) was added to a stirred solution of **22a** (10.00

g, 29 mmol) in pyridine (60 mL) maintained at 0 °C. The mixture was allowed to stand in a refrigerator overnight before being poured onto ice-cold H_2O and extracted with Et_2O to give an oil. Chromatography on a column of silica gel using a mixture of hexane and EtOAc (17:3) as eluent gave **38** (12.54 g, 90%) as an oil: IR (film) 1610, 1605, 1580, 1570, 1420 (SO_3), 1120 (SO_3) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.18 (4 H, m, CH_2), 7.10–7.50 (10 H, m, aryl *H*), 7.50–7.70 (4 H, m, aryl *H*); MS *m/z* 474 (MH^+). Anal. ($C_{24}H_{18}F_3NO_4S$) C, H, N.

Ethyl 3-[3-[2-(4,5-Diphenyl-2-oxazolyl)ethyl]phenyl]-2-propenoate (39). A mixture of **38** (11.80 g, 25 mmol), ethyl acrylate (5.01 g, 50 mmol), Et_3N (10.12 g, 100 mmol), $Pd(OAc)_2$ (0.28 g, 1.25 mmol), 1,3-bis(diphenylphosphino)propane (0.52 g, 1.25 mmol), and DMF (100 mL) was stirred at 90 °C under an atmosphere of N_2. After 2 and 6 h, additional $Pd(OAc)_2$ (0.28 g, 1.25 mmol) and 1,3-bis(diphenylphosphino)propane (0.52 g, 1.25 mmol) were added. After 22 h, the mixture was diluted with H_2O and extracted with EtOAc to give an oil which was chromatographed on a column of silica gel. Elution with a mixture hexane and EtOAc (3:1) gave **39** (9.37 g, 88%) as an oil: IR (film) 1710 (CO_2Me), 1640 (>C=C<) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.31 (3 H, t, *J* = 7 Hz, OCH_2CH_3), 3.17 (4 H, m, CH_2), 4.24 (2 H, q, *J* = 7 Hz, OCH_2CH_3), 6.41 (1 H, d, *J* = 16 Hz, CH=C*H*CO_2Et), 7.20–7.50 (10 H, m, aryl *H*), 7.50–7.80 (5 H, m, aryl *H* + C*H*=$CHCO_2Et$); MS *m/z* 424 (MH^+). Anal. ($C_{28}H_{25}NO_3$) C, H, N.

3-[3-[2-(4,5-Diphenyl-2-oxazolyl)ethyl]phenyl]-2-propenoic Acid (40). Saponification of **39** (1.50 g, 3.5 mmol) by a procedure analogous to that described for **17** gave **40** (1.40 g, 100%): mp 114–115 °C (hexane/CH_2Cl_2): IR (KBr) 1700 (CO_2H), 1640 (>C=C<) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (3 H, t, *J* = 7 Hz, CH_3 of hexane), 1.25 (4 H, m, CH_2 of hexane), 3.19 (4 H, s, CH_2CH_2-oxazole), 6.44 (1 H, d, *J* = 16 Hz, CH=C*H*CO_2H), 7.25–7.70 (14 H, m, aryl *H*), 7.75 (1 H, d, *J* = 16 Hz, C*H*=$CHCO_2H$); MS *m/z* 396 (MH^+). Anal. ($C_{26}H_{21}NO_3 \cdot 0.6C_6H_{14} \cdot 0.2H_2O$) C, H, N.

Ethyl 3-[2-(4,5-Diphenyl-2-oxazolyl)ethyl]benzenepropanoate. A solution of **39** (1.02 g, 2.4 mmol) in EtOAc (50 mL) was hydrogenated over 10% Pd on C (0.06 g) at 35 psi using a Parr hydrogenation apparatus. After 27 h, the mixture was filtered and concentrated and the residue subjected to chromatography on a column of silica gel using a mixture of EtOAc and hexane (9:1) as eluent. Elution gave the title compound (0.92 g, 90%): IR (film) 1760 (CO_2Et) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (3 H, t, *J* = 7 Hz, OCH_2CH_3), 2.59 (2 H, t, *J* = 8 Hz, CH_2CO_2Et), 2.93 (2 H, t, *J* = 8 Hz, $CH_2CH_2CO_2Et$), 3.14 (4 H, s, CH_2CH_2-oxazole), 4.11 (2 H, q, *J* = 7 Hz, OCH_2CH_3), 7.00–7.50 (10 H, m, aryl *H*), 7.50–7.70 (4 H, m, aryl *H*); MS *m/z* 426 (MH^+). Anal. ($C_{28}H_{27}NO_3$) C, H, N.

3-[2-(4,5-Diphenyl-2-oxazolyl)ethyl]benzenepropanoic Acid (41). Hydrolysis of ethyl 3-[2-(4,5-diphenyl-2-oxazolyl)-ethyl]benzenepropanoate (1.85 g, 4.3 mmol) by the procedure described for the preparation of **17** gave **41** (1.58 g, 91%): mp 119–120 °C (hexane/CH_2Cl_2); IR (KBr) 1720 (CO_2H) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.64 (2 H, t, *J* = 8 Hz, CH_2CO_2H), 2.93 (2 H, t, *J* = 7 Hz, $CH_2CH_2CO_2H$), 3.14 (4 H, s, CH_2CH_2-oxazole), 7.05–7.50 (10 H, m, aryl *H*), 7.50–7.75 (4 H, m, aryl *H*); MS *m/z* 398 (MH^+). Anal. ($C_{26}H_{23}NO_3$) C, H, N.

3-[(4,5-Diphenyl-2-oxazolyl)methoxy]benzaldehyde (43). Alkylation of 3-hydroxybenzaldehyde (9.34 g, 76 mmol) with **42** (26.72 g, 85 mmol) under conditions described for the preparation of **24c** afforded **43** (21.16 g, 70%) after chromatography on silica gel (hexane/Et_2O 2:1): mp 72–75 °C (CH_2Cl_2/hexane). IR (KBr) 1695 (CHO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.28 (2 H, s, CH_2-oxazole), 7.30–7.80 (14 H, m, aryl *H*), 9.99 (1 H, s, C*H*O); MS *m/z* 356 (MH^+). Anal. ($C_{23}H_{17}NO_3$) C, H, N.

Methyl 3-[3-[(4,5-Diphenyl-2-oxazolyl)methoxy]-phenyl]-2-propenoate (44). NaH (2.57 g of a 60% dispersion 64 mmol) was washed with hexane and covered with DME (250 mL), and trimethyl phosphonoacetate (10.71 g, 9.52 mL, 59 mmol) added dropwise. The mixture was stirred at room temperature for 15 min and a solution of **43** (19.00 g, 53 mmol) in DMF (50 mL) added in one portion. The mixture was stirred for 30 min before being diluted with H_2O and extracted with CH_2Cl_2 to give an oil. Trituration with a mixture of hexane and Et_2O gave **44** (27.20 g, 78%): mp 88–90 °C (^{i}PrOH); IR (KBr) 1715 (CO_2Me), 1645 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.85 (3 H, s, CO_2CH_3), 5.27 (2 H, s, OCH_2), 6.49 (1 H, d, *J* = 16 Hz, CH=C*H*CO_2Me), 7.10–7.55 (10 H, m, aryl *H*), 7.60–7.80 (5 H, m, aryl *H* + C*H*=$CHCO_2Me$); MS *m/z* 412 (MH^+). Anal. ($C_{26}H_{21}NO_4$) C, H, N.

3-[3-[(4,5-Diphenyl-2-oxazolyl)methoxy]phenyl]-2-propenoic Acid (45). A sample of **44** (3.00 g, 7.2 mmol) was saponified according to the procedure described for **17** to give **45** (2.25 g, 77%): mp 145–147 °C (hexane/CH_2Cl_2); IR (KBr) 1700 (CO_2H), 1640 ()C=C() cm^{-1}; ^1H NMR ($CDCl_3$/DMSO-d_6) δ 5.24 (2 H, s, OCH_2), 6.46 (1 H, d, *J* = 16 Hz, CH=C*H*CO_2H), 7.09 (1 H, dd, *J* = 8 Hz, *J'* = 2 Hz, aryl *H* ortho to O), 7.17 (1 H, d, *J* = 8 Hz, aryl *H* para to O), 7.25 (1 H, d, *J* = 2 Hz, aryl *H* ortho to O), 7.30–7.50 (7 H, m, aryl *H*), 7.60–7.80 (5 H, m, aryl *H* + C*H*=$CHCO_2H$); MS *m/z* 398 (MH^+). Anal. ($C_{25}H_{19}NO_4 \cdot 0.1H_2O$) C, H, N.

Methyl 3-[3-[(4,5-Diphenyl-2-oxazolyl)methoxy]phenyl]-propanoate. Alkylation of methyl 3-(3-hydroxylphenyl)-propanoate (5.73 g, 3 mmol) with **42** (10.00 g, 3 mmol) under conditions described for the preparation of **24p** furnished methyl 3-[3-[(4,5-diphenyl-2-oxazolyl)methoxy]phenyl]propanoate (10.34 g, 78%) as an oil after chromatography on a column of silica gel using a mixture of hexane and Et_2O (3:1) as eluent: IR (film) 1740 (CO_2Me) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.63 (2 H, t, *J* = 8 Hz, $CH_2CO_2CH_3$), 2.95 (2 H, t, *J* = 8 Hz, $CH_2CH_2CO_2CH_3$), 3.65 (3 H, s, CO_2CH_3), 5.19 (2 H, s, OCH_2), 6.80–7.05 (3 H, m, aryl *H* ortho and para to O), 7.20–7.55 (7 H, m, aryl *H*), 7.60–7.80 (4 H, m, aryl *H*); MS *m/z* 414 (MH^+). Anal. ($C_{26}H_{23}NO_4$) C, H, N.

3-[3-[(4,5-Diphenyl-2-oxazolyl)methoxy]phenyl]propanoic Acid (46). Saponification of methyl 3-[3-[(4,5-diphenyl-2-oxazolyl)methoxy]phenyl]propanoate (6.00 g, 14.5 mmol) as described for **17** gave **46** (4.15 g, 71%): mp 118–120 °C (hexane/CH_2Cl_2); IR (KBr) 1730 (CO_2H) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.67 (2 H, t, *J* = 8 Hz, $CH_2CH_2CO_2H$), 2.95 (2 H, t, *J* = 8 Hz, $CH_2CH_2CO_2H$), 5.22 (2 H, s, OCH_2), 6.80–7.00 (3 H, m, aryl *H* ortho and para to O), 7.15–7.50 (7 H, m, aryl *H*), 7.55–7.80 (4 H, m, aryl *H*), 10.71 (1 H, bs, CO_2H); MS *m/z* 400 (MH^+). Anal. ($C_{25}H_{21}NO_4 \cdot 0.11H_2O$) C, H, N.

Methyl (3-Acetoxyphenoxy)acetate (48). Alkylation of resorcinol monoacetate (20.00 g, 0.13 mol) with methyl bromoacetate under the conditions described for the preparation of **24p** gave an oil which was dissolved in MeOH (350 mL). Concentrated HCl (2 mL) was added and the mixture stirred at reflux for 20 min. The solution was concentrated, diluted with H_2O, and extracted with CH_2Cl_2 to give an oil which was distilled at reduced pressure to furnish **48** (15.98 g, 66%): bp 154–180 °C (1.5 mmHg).

Methyl [3-[(4,5-Diphenyl-2-oxazolyl)methoxy]phenoxy]-acetate. A mixture of **42** (6.68 g, 21 mmol), **48** (3.87 g, 21 mmol), K_2CO_3 (3.52 g, 25 mmol), KI (catalytic amount), and CH_3CN (125 mL) was stirred at reflux for 40 min. The mixture was cooled and filtered and the solvent evaporated to leave an oil. Chromatography on a column of silica gel using a mixture of hexane and Et_2O (3:1) as eluent furnished methyl [3-[(4,5-diphenyl-2-oxazolyl)methoxy]phenoxy]acetate (6.45 g, 72%) as an oil: IR (film) 1770 (CO_2CH_3) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.77 (3 H, s, CO_2CH_3), 4.61 (2 H, s, OCH_2-oxazole), 5.17 (2 H, s, $OCH_2CO_2CH_3$), 6.55 (1 H, dd, *J* = 8 Hz, *J'* = 2 Hz, aryl *H* ortho to O), 6.65 (1 H, m, aryl *H* ortho to O), 6.72 (1 H, dd, *J* = 8 Hz, *J'* = 2 Hz, aryl *H* ortho to O), 7.20 (1 H, t, *J* = 8 Hz, aryl *H* meta to O), 7.30–7.50 (6 H, m, aryl *H*), 7.50–7.70 (4 H, m, aryl *H*); MS *m/z* 416 (MH^+). Anal. ($C_{25}H_{21}NO_5 \cdot 0.2H_2O$) C, H, N.

[3-[(4,5-Diphenyl-2-oxazolyl)methoxy]phenoxy]acetic Acid (49). A sample of methyl [3-[(4,5-diphenyl-2-oxazolyl)-methoxy]phenoxy]acetate (5.85 g, 14 mmol) was saponified according to the procedure described for **17** to give **49** (2.70 g, 47%): mp 133–135 °C ($CHCl_3$/Et_2O/MeOH/hexane); IR (KBr) 1740, 1610 cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.47 (2 H, s, OCH_2CO_2H), 5.29 (2 H, s, OCH_2-oxazole), 6.54 (1 H, d, *J* = 8 Hz, aryl *H* ortho to O), 6.68 (2 H, m, aryl *H* ortho to O), 7.20 (1 H, t, *J* = 8 Hz, aryl *H* meta to O), 7.30–7.80 (14 H, m, aryl *H* + CO_2H); MS *m/z* 402 (MH^+). Anal. ($C_{24}H_{19}NO_5 \cdot 0.6H_2O$) C, H, N.

Methyl [3-[[(4,5-Diphenyl-2-oxazolyl)thio]methyl]phenoxy]acetate. NaH (1.00 g of a 60% dispersion in mineral oil, 25 mmol) was added to a solution of **50** (5.70 g, 23 mmol) in DMF (100 mL). After stirring at room temperature for 30 min, the mixture was cooled to 0 °C and a solution of methyl [3-(bromomethyl)phenoxy]acetate (6.50 g, 2.5 mmol) in DMF (10 mL) added dropwise. The mixture was stirred at 0 °C for 1 h and at room temperature for 2 h before being diluted with H_2O and extracted

with Et_2O. The residual oil was chromatographed on a column of silica gel using a mixture of hexane and EtOAc (2:1) as eluent to give the title compound (1.50 g, 15%): IR (KBr) 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.73 (3 H, s, CO_2CH_3), 4.40 (2 H, s, CH_2), 4.56 (2 H, s, CH_2), 6.78 (1 H, dd, J = 8 Hz, J' = 2 Hz), 6.99 (1 H, d, J = 2 Hz), 7.04 (1 H, d, J = 8 Hz), 7.20–7.40 (7 H, m), 7.45–7.60 (4 H, m); MS m/z 430 (MH^+). Anal. ($C_{25}H_{21}NO_4S$) C, H, N.

[3-[[(4,5-Diphenyl-2-oxazolyl)thio]methyl]phenoxy]acetic Acid (52). Saponification of methyl [3-[[(4,5-diphenyl-2-oxazolyl)thio]methyl]phenoxy]acetate (1.10 g, 2.6 mmol) under the conditions described for **17** gave **52** (0.60 g, 56%): mp 136–137 °C after extractive workup and chromatography on a column of silica gel using CH_2Cl_2 and MeOH (19:1) as eluent; IR (KBr) 2500, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.42 (2 H, s, OCH_2), 4.61 (2 H, s, CH_2), 6.82 (1 H, dd, J = 8 Hz, J' = 2 Hz), 7.03 (1 H, s), 7.08 (1 H, d, J = 8 Hz), 7.20–7.40 (7 H, m), 7.50–7.65 (4 H, m); MS m/z 418 (MH^+). Anal. ($C_{24}H_{19}NO_4S$) C, H, N.

2-[3-[2-(4,5-Diphenyl-2-oxazolyl)ethyl]phenoxy]acetonitrile. A mixture of **22a** (1.50 g, 4.3 mmol), bromoacetonitrile (0.58 g, 4.8 mmol), K_2CO_3 (0.73 g, 5.2 mmol), KI (catalytic amount), and CH_3CN (45 mL) was stirred and refluxed for 24 h. Additional bromoacetonitrile (0.58 g, 4.8 mmol) and K_2CO_3 (0.73 g, 5.2 mmol) were added, and the mixture was heated at reflux for 19 h. The mixture was cooled, filtered, and concentrated and the residue chromatographed on a column of silica gel. Elution with a mixture of $CHCl_3$ and MeOH (97:3) gave the title compound (1.65 g, 98%) as an oil: IR (film) 1600, 1580, 1490, 1450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.15 (4 H, s, CH_2CH_2-oxazole), 4.70 (2 H, s, OCH_2CN), 6.80–6.95 (2 H, m, aryl H ortho to O), 6.97 (1 H, d, J = 8 Hz, aryl H para to O), 7.20–7.50 (7 H, m, aryl H), 7.50–7.70 (4 H, m, aryl H); MS m/z 381 (MH^+).

5-[[3-[2-(4,5-Diphenyl-2-oxazolyl)ethyl]phenoxy]methyl]-1*H*-tetrazole (53). A mixture of 2-[3-[2-(4,5-diphenyl-2-oxazolyl)ethyl]phenoxy]acetonitrile (1.60 g, 4.2 mmol) and tri-*n*-butyltin azide (1.45 g, 4.4 mmol) was stirred at 140 °C under an atmosphere of N_2. After 20 h, the mixture was cooled and diluted with EtOAc (300 mL) and 1 N HCl (200 mL), and the mixture stirred at room temperature for 2 h. The aqueous phase was separated, the organic phase added to 0.1 M KF solution, and the mixture stirred overnight. The organic layer was separated, washed with H_2O and saturated NaCl solution, dried over Na_2SO_4, and concentrated in vacuo. The residue was chromatographed on a column of silica gel using a mixture of $CHCl_3$ and MeOH (10:1) as eluent to give **53** (1.18 g, 66%): mp 138.5–140 °C (hexane/CH_2Cl_2); IR (KBr) 1610, 1595, 1450 cm^{-1}; ^1H NMR ($CDCl_3$/DMSO-d_6) δ 2.91 (4 H, s, CH_2CH_2-oxazole), 5.13 (2 H, s, OCH_2), 6.55–6.70 (3 H, m, aryl H ortho and para to O), 6.90–7.20 (7 H, m, aryl H), 7.30–7.50 (4 H, m, aryl H); MS m/z 424 (MH^+). Anal. ($C_{25}H_{21}N_5O_2$) C, H, N.

Methyl 4-[3-(4,5-Diphenyl-2-oxazolinyl)propoxy]benzoate (56b). 4-Bromobutyryl chloride (9.63 g, 6.01 mL, 50 mmol) was added dropwise to a stirred solution of **13** (10.00 g, 47 mmol) and pyridine (4.47 g, 4.56 mL, 56 mmol) in CH_2Cl_2 (250 mL) maintained at 0 °C. After completing the addition, the mixture warmed to room temperature and pyridine (0.89 g, 0.9 mL, 11 mmol) was added followed by 4-bromobutyryl chloride (1.93 g, 1.2 mL, 11 mmol). The mixture was stirred at room temperature for 1 h, poured onto H_2O, and extracted with CH_2Cl_2 to give an oil which was dissolved in DMF (220 mL). K_2CO_3 (7.80 g, 56 mmol), KI (catalytic quantity), and methyl 4-hydroxybenzoate (7.88 g, 52 mmol) were added, and the mixture was stirred at 110 °C under an atmosphere of N_2 for 1 h. The mixture was cooled, diluted with H_2O, and extracted with Et_2O to give an oil which was dissolved in AcOH (120 mL). NH_4OAc (18.15 g, 0.235 mol) was added and the mixture heated at reflux for 75 min. The solution was cooled, poured onto H_2O, and extracted with CH_2Cl_2 to give an oil which was subjected to chromatography on a column of silica gel. Elution with a mixture of hexane and Et_2O (3:2) furnished **56b** (11.25 g, 57%): mp 85–87 °C (hexane/Et_2O); IR (KBr) 1740 (CO_2Me) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.36 (2 H, quintet J = 7 Hz, CH_2CH_2O), 3.06 (2 H, t, J = 7 Hz, CH_2-oxazole), 3.86 (3 H, s, CO_2CH_3), 4.16 (2 H, t, J = 7 Hz, OCH_2), 6.89 (2 H, d, J = 8.5 Hz, aryl H ortho to O), 7.20–7.45 (6 H, m, aryl H), 7.50–7.75 (4 H, m, aryl H), 7.96 (2 H, d, J = 8.5 Hz, aryl H meta to O); MS m/z 414 (MH^+). Anal. ($C_{26}H_{23}NO_4$) C, H, N.

4-[3-(4,5-Diphenyl-2-oxazolyl)propoxy]benzoic Acid (57b). A mixture of **56b** (8.00 g, 19 mmol), 5 N NaOH solution (11.62 mL), and MeOH (150 mL) was stirred at reflux for 1.5 h. The solvent was removed in vacuo, and the residue diluted with H_2O and 2 N HCl solution to precipitate a white solid which was filtered off and air-dried. Recrystallization from ^{i}PrOH afforded **57b** (7.25 g, 93%): mp 181–183 °C; IR (KBr) 1685 (CO_2H), 1600 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.23 (2 H, t, J = 7 Hz, CH_2CH_2O), 2.99 (2 H, t, J = 7 Hz, CH_2-oxazole), 4.17 (2 H, t, J = 7 Hz, OCH_2), 6.99 (2 H, d, J = 8.5 Hz, aryl H ortho to O), 7.20–7.65 (10 H, m, aryl H), 7.85 (2 H, d, J = 8.5 Hz, aryl H meta to O), 12.61 (1 H, s, CO_2H); MS m/z 400 (MH^+). Anal. ($C_{25}H_{21}NO_4$) C, H, N.

Biological Evaluation. Blood platelet aggregometry and radioligand binding studies were performed according to protocols described previously.[21,23]

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